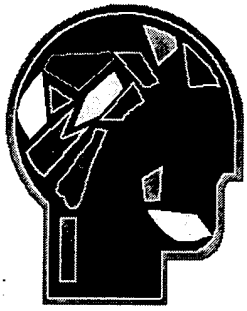

Classification of Headache

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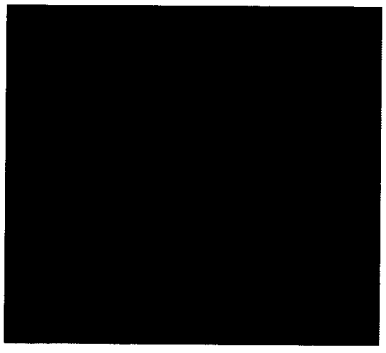
Most of the research work published in the past was difficult to interpret because there were no clearly defined criteria established for the diagnosis of different types of **headache**. This problem was addressed by the International **Headache** Society (IHS) in 1988 when the "**Classification** and Diagnostic Criteria for **Headache** Disorders, Cranial Neuralgias and Facial Pain" was published. All the publications subsequent to that have relied on these criteria for the diagnosis of various **headache** syndromes. A familiarity with this **classification** will be worthwhile. Some aspects of the **classification** and diagnostic criteria will be detailed in the following sections.

13 general groupings of headache disorders



1. Migraine
2. Tension-type **Headache**
3. Cluster **Headache** and Chronic Paroxysmal Hemicrania
4. Miscellaneous headaches unassociated with structural lesions
5. **Headache** associated with head trauma
6. **Headache** associated with vascular disorders.
7. **Headache** associated with non-vascular

intracranial disorder
8. Headache associated with substances or their withdrawal
9. Headache associated with non-cephalic infections.
10. Headaches associated with metabolic disorders
11. Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures.
12. Cranial neuralgias, nerve trunk pain and deafferentation pain
13. Non-classifiable Headache

Migraine

Classification

Phases of migraine

Premonitory Phase

This phase of the migraine attack occurs hours to one or two days prior to the onset of the actual headache in both groups of migraine headache patients. The symptoms most commonly reported are hyperactivity, hypoactivity, depression, craving for special foods, repetitive yawning or similar atypical symptoms.

Prodromal Phase

This phase is most often associated with the aura in migraine patients with aura. There is no universally accepted prodromal phase for migraine without aura.

Headache Phase

This phase describes the onset of actual pain. The headache phase typically lasts from 2 to 72 hours, may be unilateral (60%)or bilateral.

Postdromal Phase

After the h adache attack patients often report feeling "washed out", irritable, listless,weak, impaired concentration, aching, reduced or increased appetite, euphoria or hypomania.

Incidence: Current epidemiological studies conclude that approximately 16% of females and 7% of males in the United States suffer from migraine **headache**. Most workers believe that this is a gross underestimation. There is no evidence for any socioeconomic differences in the incidence of migraine.

Pathogenesis: There is increasing evidence that migraine is a genetically determined disorder. Recent studies report that the defective gene is located on chromosome 19 in familial hemiplegic migraine. Until the actual gene is identified and its messenger defined we cannot be certain about the actual pathogenesis. However there is enough information available currently to support the hypothesis that the neurotransmitter serotonin is involved in the pathogenesis and that the serotoninergic neurons influence the trigeminovascular system which in turn leads to dilation and neurogenic inflammation of the blood vessels. This knowledge base is expanding rapidly especially since the introduction of designer drugs like sumatriptan for the treatment of migraine.

Classification

Note: If a patient fulfils criteria for more than one type of migraine, all types should receive a diagnosis. In other words, different types of migraine are not mutually exclusive. If the onset of the migraine occurs at the approximate time of one of the **headache** disorder from 5-11, that condition should be listed as the primary **headache** diagnosis. If the migraine is only aggravated by one of the conditions 5-11, then the migraine is noted as the primary diagnosis and the other condition is noted as an aggravating factor. Don't use the term "common" or "classic" to describe migraine. These terms have been replaced by the terms "migraine without aura", and "migraine with aura". Most migraine patients have attacks without aura. Those migraineurs who have migraine almost exclusively with aura will also have attacks without aura.

1. Migraine

Following is the currently approved IHS **classification** of migraine.

1.1 Migraine without aura

1.2 Migraine with aura

1.2.1 Migraine with typical aura

1.2.2Migraine with prolonged aura

1.2.3Familial hemiplegic migraine

1.2.4Basilar migraine

1.2.5 Migraine aura without **headache**

1.4 Retinal Migraine

1.5 Childhood periodic syndromes that may be precursors to or associated with migraine

1.5.1 Benign paroxysmal vertigo of childhood

1.5.2 Alternating hemiplegia of childhood

1.6 Complications of migraine

1.6.1 Status migrainosus

1.6.2 Migrainous infarction

1.7 Migrainous disorder not fulfilling above criteria

Classification Criteria for Migraine without aura

Idiopathic **headache** disorder manifesting attacks that last 4-72 hours. Typical characteristics of the **headache** are unilateral pulsating quality of pain with moderate to severe intensity. The pain is typically aggravated by routine physical activity and associated with nausea, photophobia and phonophobia.

A. At least five attacks fulfilling B-D.
B. **Headache** lasting 4-72 hours (untreated or unsuccessfully treated).
C. **Headache** has at least two of the following characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe intensity (inhibits or prohibits daily activities)
    4. Aggravation by walking stairs or similar routine physical activity.
D. During **headache**, at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. At least one of the following
    1. History, physical, and neurological examinations do not suggest one of the disorders listed in groups 5-11.
    2. History and/or physical and/or neurological examination do suggest such disorder, but it is ruled out by appropriate investigations.

3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Classification of Migraine with aura

Idiopathic recurring disorder manifesting with attacks of neurological symptoms unequivocally localizable to cerebral cortex or brain stem. These symptoms gradually develop over 4-20 minutes and usually last less than 60 minutes. **Headache**, nausea and/or photophobia usually follow neurological aura symptoms directly or after a free interval of less than an hour. The **headache** usually lasts 4-72 hours but may be completely absent (migraine equivalent).

A. At least two attacks fulfilling B.
B. At least three of the following four characteristics:
    1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brainstem dysfunction.
    2. At least one aura symptom develops gradually over more than 4 minutes or two or more symptoms occur in succession.
    3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.
    4. **Headache** follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura).
C. At least one of the following:
    1. History, physical and neurological examinations do not suggest one of the disorders listed in groups 5-11.
    2. History, physical, and neurological examination do suggest such disorder, but it is ruled out by appropriate investigations.
    3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Classification of Migraine with typical aura

Migraine with an aura consisting of homonymous visual disturbances, hemisensory symptoms, hemiparesis or dysphasia or combinations thereof. Gradual development,duration under one hour or complete reversibility characterize the aura which is associated with **headache**.

A. Fulfills criteria for migraine with aura, including all four criteria under B.
B. One or more aura symptoms of the following types:
    1. Homonymous visual disturbance.
    2. Unilateral paresthesias and/or numbness
    3. Unilateral weakness
    4. Aphasia or unclassifiable speech difficulty.

Tension-type Headache

Incidence : The actual incidence of tension-type **h adache** is not known. Mild and intermittent varieties of tension-type **headache** is very frequent and most of the sufferers do not seek medical care. This is thought to be the most common form of **headache**. Chronic variety of tension-type **headach** can be disabling and require long term

treatment. This occurs at least as frequently as migraine headache.

Pathogenesis: Exact pathogenesis is unknown. It is believed that there is an alteration of central nociceptive system which leads to the development of this type of headach . However peripheral mechanisms in the scalp muscles may play a role in generating the symptoms. Some of the recent neurophysiological studies reveal abnormalities in the polysynaptic brainstem pathways but it is not clear how exactly this leads to the development of tension-type headache. Emotional and psychological problems are assumed to play a significant role in its pathogenesis.

Classification of Tension-Type Headache:

2. Tension-type headache

2.1 Episodic tension-type headache

2.1.1 Episodic tension-type headache associated with disorder of pericranial muscles

2.1.2 Episodic tension-type headache unassociated with disorder of pericranial muscles

2.2 Chronic tension-type headache

2.2.1 Chronic tension-type headache associated with disorder of pericranial muscles

2.2.2 Chronic tension-type headache unassociated with disorder of pericranial muscles

2.3 Headache of the tension-type not fulfilling above criteria

The term "disorder of pericranial muscles" denotes the presence of tenderness in these muscles.

2.1. Episodic Tension-type headache:

Clinical features & Diagnosis: Recurrent episodes of headache lasting minutes to days. The pain is typically pressing/tightening in quality, of mild or moderate intensity, bilateral in location and does not worsen with routine physical activity. Nausea is absent, but photophobia or phonophobia may be present. Episodic tension type headache is very common and is self-limited. However a certain percentage of patients experience these headaches more and more frequently and progress to the chronic variety. Following are the diagnostic criteria:

A. At least 10 previous **headache** episodes fulfilling criteria B-D listed below. Number of days with such **headache** <180/year (<15/month).
B. **Headache** lasting from 30 minutes to 7 days.
C. At least 2 of the following pain characteristics:
    1. Pressing/tightening (non-pulsating) quality
    2. Mild or moderate intensity (may inhibit, but does not prohibit activities).
    3. Bilateral location
    4. No aggravation by walking stairs or similar routine physical activity

Both of the following:

1. No nausea or vomiting (anorexia may occur)
2. Photophobia and phonophobia are absent, or one but not the other is present.

At least one of the following:

1. History, physical and neurological examinations do not suggest one of the disorders listed in groups 5-11.
2. History and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations.
3. Such disorder is present, but tension-type **headache** does not occur for the first time in close temporal relation to the disorder.

2.2 Chronic tension-type **headache**:

Average **headache** frequency 15 days/month (180/year) for 6 months or longer fulfilling criteria B-D listed below.

At least 2 of the following pain characteristics:

1. Pressing/tightening (non-pulsating) quality.
2. Mild or moderate intensity (may inhibit, but does not prohibit activities).
3. Bilateral location
4. No aggravation by walking stairs or similar routine physical activity

Both of the following:

1. No vomiting.
2. No more than one of the following: Nausea, photophobia or phonophobia

There is no evidence of an underlying disorder by history, physical,

neurological examination and, if necessary after appropriate investigations to rule out such underlying disorders which might cause similar **headache** (summary of the actual wording used by IHS **classification**).

Treatment of tension-type **headache**:

Tricyclic antidepressants (low dose therapy, 10-80 F mg.)

Muscle relaxants (intermittent use during flare-ups, consider cyclobenzaprine 10-30mg.)

Anti-inflammatory agents

Analgesics (for short term 1-2 weeks only if needed, while stabilizing patient)

Use Myofascial Pain Protocol including stretching, Fluorimethane Spray & Stretch, moist heat and ice.

Behavior modification therapy, biofeedback, stress management.

Cluster **Headache** and Chronic Paroxysmal Hemicrania

3.1 Cluster **Headache**.

A. At least 5 attacks fulfilling B-D
B. Severe unilateral orbital, supraorbital and /or temporal pain lasting 15-180 minutes untreated.
C. **Headache** is associated with at least one of the following signs which have to be present on the pain-side:
    1. Conjunctival injection
    2. Lacrimation
    3. Nasal congestion
    4. Rhinorrhea
    5. Forehead and facial sweating
    6. Miosis
    7. Ptosis
    8. Eyelid edema
D. Frequency of attacks: from 1 every other day to 8 per day
E. At least one of the following:
    1. History, physical, and neurological examinations do not suggest one of the lisorders listed in groups 5-11.
    2. History and/or physical and/or neurological examinations do suggest

[redacted]

such disorder, but it is ruled out by appropriate investigations.
3. Such disorder is present, but cluster **headache** does not ocur for the firt time in close temporal relation to the disorder.

Episodic cluster **headache** occurs in periods lasting 7 days to one year separated by pain free periods lasting 14 days or more. Cluster periods usually last between 2 weeks and 3 months.

3.1 Chronic Cluster Headache.

Chronic cluster **headache** is diagnosed if the attacks occur for more than one year without remission or with remissions lasting less than 14 days.

3.2 Chronic Paroxysmal Hemicrania

The variant form called "chronic paroxysmal hemicrania" (CPH) predominantly occurs in females. Daily frequency is much higher (average cluster **headache** frequency is 1-2/day whereas in CPH the average is more than 8/day) and the duration is much shorter. Other characteristics are the same except that his variety of **headache** responds dramatically to treatment with indomethacin. Alcohol appears to be the only consistent triggering factor, if ingested during the **headache** cycle but not in between.

Management: Unlike migraines, most cluster **headache** patients require specific therapy because the pain is excruciating.

Abortive treatment of cluster headache:

- Oxygen inhalation (100% oxygen at 7-10 liters/min. for 15 min.)
- Sumatriptan (6mg. sc.) or DHE-45 (1mg I.M.)
- Ergotamine preparations (1-2 mg.)
- Analgesics and anti-inflammatory agents (rarely useful and can cause rebound phenomenon)

Prophylactic treatment of cluster headache

[redacted]

3.1.2 Episodic Cluster headache

Methysergide (4-6 mg/day, maximum 6 months)

Calcium channel blockers (verapamil 240-480 mg./day)

Steroids (short course with rapid taper, 40-60 mg./day for 2 weeks)

Lithium carbonate (dose to attain usual therapeutic range)

Ergotamine tartarate (2-4 mg./day for a short period)

Indomethacin (75-150 mg./day for CPH)

3.1.3 Chronic cluster headache

Lithium carbonate (dose to attain usual therapeutic range)

Verapamil (240-480 mg./day)

Intermittent courses of methysergide or prednisone

Temporary or permanent denervation of trigeminal nerve

A small percentage of chronic cluster **headache** patients may become resistant to all forms of medical therapy. In this situation, selective lesions made in the Trigeminal pain pathways may have to be used for pain relief.

Generational Health™

Learn more:

Alzheimer's Disease
Arthritis
Breast Cancer
Colon and Rectal Cancer
Depression
Diabetes
High Blood Pressure
High Cholesterol
Migraine
Ovarian, Cervical and Uterine Cancer
Prostate Cancer

For Further Information

Migraine

Many people have had some of the symptoms of migraine headaches, such as an intense throbbing pain in the forehead or temple. But people diagnosed with migraines experience recurrent disabling attacks, with pain most often occurring in one side of the head that can last from several hours to several days. Various combinations of symptoms, such as nausea, vomiting, and sensitivity to light and sound, may accompany these attacks. Since physical activity makes the headaches worse, migraines often cause sufferers to miss work or school. Some people experience warning symptoms before an attack. These symptoms are called an aura and may include seeing flashing lights, disturbances in vision, speech difficulty, weakness in an arm or leg, tingling of the face or hands, or confusion.

The Cause: Heredity and Other Factors
People with migraines tend to have relatives with the condition. They may be at a higher-than-average risk for developing migraines if the disorder already affects their parents or siblings. Some researchers believe that migraine sufferers have a nervous system that is more sensitive to triggers such as stress, intense emotion, fatigue, weather, or certain foods. This sensitivity may result in the inflammation of blood vessels and nerve endings in the brain. However, more investigation is needed to define the role of heredity more clearly.

What You Can Do (return to top)
Doctors don't have a test to diagnose migraines. If you've had migraine-like symptoms or ever develop them, your family history will be used to determine if you have migraine headaches. Although migraines are not curable, they can often be managed with medication.

Learn More: (return to top)

- *Journal of the American Medical Association's* Migraine Information Center, including The Genetics of Migraine news brief
- National Institute of Neurological Diseases and Stroke, including a symptom and treatment summary, from this branch of the National Institutes of Health

The health information contained herein is for educational purposes only and is not intended to replace individualized medical advice and discussions with a healthcare provider. All decisions regarding patient care must be made by a healthcare provider, who will consider the unique characteristics of the patient.

The information on this site is intended for US residents only.

Generational Health is a resource developed by Pfizer Women's Health.

Signs and symptoms of migraine

Migraine pain differentiates from other types of headache, it has specific **symptoms**. These **symptoms** appear different from person to person in intensity, character, frequency and duration. **Migraine** attacks can appear as infrequently as a couple of times a year or almost every day. There are two main types of **migraine**: Classical **Migraine** - **migraine** with aura- and Common **Migraine** - **migraine** without no warning or aura.

A minority of **migraine** patients experience aura, which is the term for the sign of the pain to come. The sign can be described as bright spots or zigzag lines before the eyes and blurred vision or temporary visual loss. In rare cases numbness or tingling of the face and lips can be observed. These **symptoms** usually go away within one hour and replaced by a headache. But it also possible to have the aura and not the pain that comes after.

With the common **migraine**, headache begins without warning. Children mostly experience common **migraine**. Common **symptoms** of **migraine** are associated with:

-Intense head pain. The pain begins on one side of the head and it spreads downward to the eye, face and even neck. The pain can switch sides and less commonly can affect both sides at once.

-Feeling a relentless throbbing or pounding deep in the head.

-Having nausea

-Vomiting

-Strong and painful reactions to light and loud noises. As a result patients try to avoid them.

-The simple act of moving may be difficult during the **migraine** attack. Pain may worsen from activity.

-Not being able to carry out day to day activities.

-Need to lie down during the attacks.

It is not necessary to have all these **sympt ms**. They may be moderate or severe. **Migraine** attacks may last between four hours and three days if not treated or poorly treated. Because you have the need to lie down and rest during these attacks your working

life, family life and social activities may be disrupted.

Migraines most commonly occur in women and usually start between the ages of 10 and 46. Migraines can be difficult to diagnose. Without proper diagnosis, the patient cannot get the proper treatment. It is more likely the patient visits the doctor headache-free so it is important to describe the **sympt ms** in a very clear way.

Because **migraine** is more than a common headache, in some people painkillers may not work. It is more suitable to take special **migraine** medicines prescribed by a doctor These medicines can stop or help to relieve the **migraine** pain.

Title: Signs and **symptoms** of **migraine**
Description: Almost everyone gets a headache, but **migraine** is not just a bad headache. It has specific **symptoms**.

Recognizing The Symptoms

The two main types of ***Migraine*** are known as:

MIGRAINE WITH AURA

In this form of ***Migraine***, the headache is preceded by an *aura*. This may start 15-60 minutes before the headache. The *aura* may have visual disturbances, such as **flashing lights**, **zig-zags**, **varying colors**, and possibly **loss of vision**. There may also be a **tingling** or **numbness** on one side of the face with **pain around the eye**.

Migraine **with** *aura* has **symptoms** prior to the start of the headache. These are less common than *Migraines* **without** *aura*.

MIGRAINE WITHOUT AURA

Migraines **without** *aura* do not start with the **symptoms** shown above.
The period after recovery may leave a general feeling of weakness, loss of appetite, and low tolerance of noise and strong smells (such as perfume).

Common **symptoms** include:

- *Abnormal sensations*
- *Irritability*
- *Scalp tenderness*
- *Nausea/vomiting*
- *Loss of appetite*
- *Double vision*
- *Blind spots*
- *Seeing "zig-zag" lines*
- *Partial blindness in one eye*
- *Facial paralysis on one side*
- *Dizziness and lightheadedness*
- *Eye muscle paralysis*
- *Light or sound sensitivity*
- *Head pain (pounding, pulsating, throbbing)*

Next Page ▶

Migraine | *What Is Migraine?* | *What Causes the Condition?*
Recognizing the Symptoms | *Diagnosing the Condition* | *Treatment*

Symptoms of Migraine Include:

DEPRESSION

Feelings of Helplessness

Vertigo

NAUSEA

Photophobia

Headache

Sensitivity to smell

Phonophobia

Ringing In Ears

Family History Of Headaches

Irritability

Difficulty Concentrating

Vomiting

Motor Disturbances

Sensitivity to Changes In Weather

Uneasiness in Crowds

easily STRESSED

Imbalance

Mood Swings

Speech Disturbances

(Note: These **symptoms** have been reported as associated with migraines from **migraine** sufferers. This section is not all-inclusive, nor is it an alternative to an examination and diagnosis from a board-certified physician. This list is not to be used to self-diagnose or treat your condition. This section is for informative purposes ONLY. If you experience any of these **symptoms**, please contact your physician for evaluation and diagnosis. These **symptoms** can be caused by many other medical problems, some serious, and ONLY your physician can provide you with an accurate diagnosis of your condition.)

Main Menu

the physician and sportsmedicine

Managing Migraines in Active People

Seymour Diamond, MD

THE PHYSICIAN AND SPORTSMEDICINE - VOL 24 - NO. 12 - DECEMBER 96

If your browser does not support tables click here.

In Brief: **Migraine** patients who are physically active may find that exercise can provoke a **migraine** attack or that regular exercise helps reduce the severity of their headaches. After the diagnosis of **migraine** has been made with a complete history and physical examination, the next steps are to identify the triggers, such as certain foods or changes in sleep schedule, and design an individualized treatment plan. If exercise is a trigger, nondrug measures such as adequate warm-up, nutrition, and hydration during activity are important. Whether the triggers are exercise-related or not, exercise and other general measures may be beneficial adjuncts to the appropriate abortive, pain-relief, or prophylactic drug regimen.

Because **migraine** is such a common disorder and because many Americans exercise regularly, it's likely that many **migraine** sufferers lead physically active lives. A **migraine** patient's exercise habits should be considered in devising a treatment plan, for several reasons. One is that vigorous exercise can trigger a **migraine** in some patients. A second is that the choice of pharmacologic therapy for **migraine** may influence the patient's ability to exercise. Finally, as a part of a balanced life-style, exercise may help prevent migraines or limit their severity.

A recent epidemiologic study (1) estimates that the prevalence of **migraine** in the general population is 23% to 29% of women and 15% to 20% of men. **Migraine** has a major impact on the economy because of lost work days, lost income, and the money spent on

medical care and drugs. Exercise, for some patients, is one more life element compromised by this condition.

Migraine has been defined by the International Headache Society (2) as an "idiopathic, recurring headache disorder manifesting in attacks lasting 4 to 72 hours. Typical characteristics of headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, and photo- and phonophobia." Most **migraine** sufferers report a family history of migraines, and a genetic model has been proposed (3).

Typically, the initial onset of **migraine** headaches occurs in adolescence or the early 20s--the period when people are most physically active. **Migraine** can occur in children as young as age 5, with a peak from 10 to 13 years (4). Seventy percent of total **migraine** sufferers are women, though in children both genders are affected equally.

Migraine Stages

Migraines may be subdivided by the presence or absence of prodromal signs that precede the attack by 10 to 20 minutes. The **aura** phase, usually consisting of transient, focal neurologic symptoms, is experienced by about 35% of **migraine** sufferers. Visual disturbances are the most common prodromal signs and include scotomata (blind spots), teichopsia (fortification spectra), photopsia (flashing lights), and visual hallucinations such as metamorphopsia. The **aura** may also consist of paresthesias, aphasia, vertigo, or ataxia. The symptoms usually resolve before the acute attack.

Patients who have **migraine** with or without **aura** may note premonitory signs starting as early as 24 hours before the acute attack. These signs include excessive fatigue or extreme energy, anorexia or increased hunger, constipation or diarrhea, pallor, chills, increased urinary frequency, or fluid retention. Patients may also note changes in mood, such as irritability, depression, euphoria, anxiety, obsessional behavior, or apathy. They may note difficulty in concentrating, excessive yawning, shakiness, or hyperosmia.

Patients who have **migraine** will describe the pain as throbbing or pulsating, usually severe, and often incapacitating. **Migraine** is considered a "sick" headache with associated symptoms such as nausea, vomiting, and photophobia. Other complaints associated with an acute attack include phonophobia, osmophobia, diarrhea, dizziness, lightheadedness, chills, and fatigue.

In some patients, attacks involving focal neurologic deficits may persist beyond the headache. Forms of this entity, called complicated **migraine**, include hemiplegic, ophthalmoplegic, basilar artery, and retinal **migraine**. These **migraine** attacks can be frightening for the patient and the treating physician.

The frequency of **migraine** attacks typically varies from 2 to 8 per month; in some patients they are less frequent. **Migraine** is not a daily headache. About 60% of female **migraine** patients report a menstrual relationship to their acute headaches (5). These patients may experience headaches only around the time of menses, such as 2 days immediately before, during the flow, or 2 days postmenses. The duration of **migraine** attacks also varies, from 4 to 72 hours.

Targeting the Triggers

A number of **migraine** triggers have been identified. Some patients are particularly sensitive to foods containing vasoactive substances, such as tyramine, and should avoid chocolate, aged cheese, pickled foods, processed meats, fermented sausage, or cultured dairy products (sour cream, yogurt). Patients who routinely consume excessive caffeine may also precipitate a **migraine** attack if they miss the caffeine-containing beverage or medication. The artificial sweetener aspartame, used extensively in low-calorie foods (diet soda and sugar-free desserts, candy, and gum), has been identified as a **migraine** trigger (6). Monosodium glutamate (MSG), used as a flavor enhancer in common prepared foods and fast foods, has long been identified with the "Chinese restaurant" syndrome. Though the syndrome has recently been discounted by a US Food and Drug Administration committee, my personal observation is that MSG can trigger acute headaches in about 20% of all **migraine** patients. These patients should be attentive to the ingredients used in their food.

Alcohol is a well-known **migraine** provocateur, with red wine being the most common (7). Because red wine does not contain significant levels of tyramine, the complex flavonoid phenols have been suggested as the culprits because they are present in smaller amounts in white than in red wines (8).

Patients who have migraines tend to be sensitive to any changes in their daily lifestyle. Stress, fatigue, oversleeping, or skipped or missed meals can all help precipitate a **migraine**. At the Diamond Headache Clinic, we advise patients to maintain a strict schedule for meals and sleep. Many patients will complain of a weekend or holiday headache that can be linked to sleeping past their usual wake-up time and missing the first cup of coffee or orange juice. We recommend that patients rise at the same time each day, drink or eat, then return to bed if they desire. With the stress of busy lifestyles and the quest for achieving and maintaining a desirable weight, individuals may skip or delay a meal. The mechanism by which hunger or hypoglycemia triggers a headache is unknown. A regular meal schedule is encouraged for those who are sensitive to missed meals (9).

When Exertion Is a Trigger

Any form of exertion--straining at stool, coughing, sneezing, orgasm, or strenuous exercise--can trigger headache in sensitive individuals. Patients who present with **migraine** triggered by exertion should be thoroughly evaluated to rule out an organic disorder, including arteriovenous malformation, Arnold-Chiari malformation, pheochromocytoma, and aneurysm; however, the cause of exertional headaches is usually benign and can be easily treated. Patients who present with exertional **migraine** should undergo a complete neurologic examination and computed tomography. Magnetic resonance imaging with gadolinium may be indicated. The criteria for ordering neuroradiologic scanning are listed in table 1.

Table 1. Criteria for Ordering Neuroradiologic Scanning in Patients With Migraine

Suspicion of cerebellar hemorrhage or infarct
Stroke in progress or completed stroke with emergency use of anticoagulants
History and examination suggestive of intracerebral hemorrhage or mass lesion
Acute signs of increased intracranial pressure
Patients at risk for cerebral abscess who require lumbar puncture
Blunt head trauma with signs of increased intracranial pressure
Depressed skull fracture
Open skull fracture
Penetrating head injury
Head injury with Glasgow coma rating less than 9

Exertional **migraine** has been linked to many factors, such as excessive fatigue, lack of adequate warm-up before exercise, dehydration, relative hypoglycemia, and exercise at high altitude. This form of headache may be triggered by moderately intense but prolonged activity and may present in patients who exert themselves in hot, humid weather. The headache may be aggravated by exposure to cold and by dyspnea (10). Headaches associated with exercise at high altitudes may occur 6 to 96 hours after exposure. Patients describe the pain of exertional headaches as throbbing and aggravated by maneuvers that increase intracranial pressure, such as coughing, running, straining at stool, Valsalva's maneuver, or orgasm.

Effort **migraine** usually occurs immediately after the exertion and lasts from 5 minutes to 24 hours. The majority of patients have a personal or family history of **migraine**. Prodromal symptoms without headache pain can also occur after exercise (11).

Cases of Exertional Migraine

An interesting description of effort **migraine** was written by Jokl (12), who experienced a headache immediately after running a mile relay in a university track championship. During his freshman year in medical school he ran the anchor leg on the mile relay team at the German track championships, finishing in a personal best of under 50 seconds in the team's victory. A few minutes after the race he developed nausea, headache, prolonged weakness,

and vomiting that lasted 15 minutes and quickly subsided.

Another report (13) focused on several runners at the Olympic Games in Mexico City in 1968. Despite the high conditioning of the athletes, they experienced scotomata, unilateral retroorbital pain, nausea, and vomiting. These episodes occurred after longer running events but not after sprints. In addition to the high altitude, heat and humidity contributed to the athletes' discomfort.

In a review from Japan, it is reported that a 51-year-old woman with no history of **migraine** experienced several unilateral headaches associated with nausea that occurred during or immediately after swimming (14). The pain was relieved by rest. Physical and neurologic examinations were negative. The physicians suggested that the pathophysiology could be attributed to changes in intracranial pressure and constriction of the intracranial blood vessels because of swimming. These changes also led to a secondary cerebral hypoxia, and eventually the headache. The authors concluded that the possible link between swimming and headache merited further study.

In another report, a 48-year-old woman complained of severe **migraine** onset within 1 hour of completing a rigorous exercise bout (15). The woman had a history of headaches, but reported she had experienced no acute attacks during 5 years of taking aerobics classes. However, in the preceding year, the headaches occurred after each exercise session. After considering all factors and undergoing neuroradiologic testing, the patient realized that these exercise-related headaches started after she switched from oral estrogen to an estrogen patch. When the patient exercised, her circulation increased, which hastened the absorption of the estrogen, resulting in a typical **migraine** attack.

Exercise as Therapy?

Persons who have a **migraine** headache seek a dark, quiet room, and the headaches are often relieved by rest. The severity of the headache and associated symptoms usually prevents the patient from participating in daily activities, including exercise, whether strenuous or mild. For some patients, however, exercise can help prevent or relieve migraines.

An anecdotal report (16) detailed the case of a 43-year-old former professional dancer who participated in a regular aerobic exercise program and noted that exercise helped abort acute **migraine** attacks. At the onset of the prodromal phase, if the opportunity afforded itself, the dancer would go for a run, which would eliminate the visual **aura** symptoms and prevent the headache. The author warned about generalizing this measure for all **migraine** sufferers, and noted that a high level of fitness may first be necessary to duplicate these results. The author also reported that the subject had a long history of participation in exercise without **migraine**.

Exercise may be recommended in a multidisciplinary treatment regimen. To promote healthy behavior, activities such as walking, jogging, or other exercise may be indicated. At the Diamond Inpatient Headache Unit, patients are encouraged to participate in an exercise program supervised by the physical therapy department.

In one study (17), 11 **migraine** sufferers participated in a 6-week cardiovascular exercise program. By the end of the program, the patients' cardiovascular fitness had improved and they reported that their **migraine** attacks were less painful. The authors thought that two

factors might have contributed to the improvement. The patients might have had certain expectations for the study, and cardiovascular exercise might have improved their mood and response to stressful stimuli. The researchers acknowledged that the results should not be generalized and that researchers should determine if longer exercise programs maintain positive outcomes.

Treatment Options

Migraine treatment can be divided into four kinds of measures: nonpharmacologic, abortive, pain relief, and prophylactic. Table 2 (see below) details the pharmacologic options for managing migraine headaches.

Nonpharmacologic measures. Nondrug strategies for managing migraines include avoiding possible triggers. Maintaining strict schedules for sleep and meals can prevent headaches related to fatigue and hunger. A balanced lifestyle is extremely important for active patients. If exercise is considered a migraine precipitant, patients should be encouraged to warm up adequately before working out. A competitive swimmer was able to reduce her headaches by quantitative warm-ups before each race (18). Progressive relaxation exercises and biofeedback techniques may be helpful for active individuals. Using these nondrug modalities before exercise might prevent effort migraine or, at least, decrease the severity of an acute headache.

Abortive therapy. In abortive therapy, the patient takes the medication at the first sign of a headache. The agent of choice for migraine abortive therapy is sumatriptan succinate. Sumatriptan is a specific 5-hydroxytryptamine1 receptor (5-HT1) subtype agonist that provides the beneficial effect of 5-HT without its side effects. Sumatriptan may be administered subcutaneously or orally and is considered an effective, safe agent in migraine abortive therapy. For patients who experience a headache immediately after exercise and are not able to take a medication immediately, sumatriptan is particularly useful because it can be used at any time during an attack. It is contraindicated in patients who have coronary artery disease, Prinzmetal's angina, or uncontrolled hypertension.

The ergot preparations have long been used as migraine abortive agents. Their efficacy depends on use early in an attack. For patients experiencing migraine with aura, the agent should be used during the prodromal phase. In the United States, ergotamine is available sublingually or in combination with caffeine in oral and rectal preparations. The sublingual form may be preferred because of its rapid onset of action. Ergotamine is not available in the United States for parenteral administration, but an ergotamine derivative, dihydroergotamine mesylate (DHE), administered subcutaneously, has been used effectively in migraine abortive therapy. The ergot preparations cannot be used daily; a 4-day hiatus must be maintained between days of use to prevent rebound headaches. Ergots cannot be used concomitantly with sumatriptan.

For patients who cannot take ergotamine or who have migraine attacks lasting more than 1 day, a combination agent containing isometheptene mucate, dichloralphenazone, and acetaminophen may be indicated. Isometheptene mucate has cerebral vasoconstrictor effects similar to those of the ergot preparations. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been effective in migraine abortive therapy because they inhibit inflammation and prostaglandin formation. The phenothiazines--chlorpromazine and prochlorperazine--are often effective as migraine abortive agents in emergency departments because of their dopaminergic and adrenergic effects. These agents can also

relieve the gastrointestinal effects of **migraine**. However, their sedative effects may not be appropriate for patients who are eager to return to vigorous activity.

Pain relief. Despite valiant efforts to abort **migraine** attacks, pain relief measures may be required. Narcotic analgesics should be avoided in patients who have frequent attacks because of the addiction potential. An excellent alternative is the NSAID ketorolac tromethamine, which is available for parenteral administration. Transnasal butorphanol tartrate also has been effective in relieving the pain of **migraine**. Phenothiazines may be used to relieve the associated symptoms of a **migraine** attack. Metoclopramide hydrochloride, believed to enhance the absorption of oral medications, has limited sedative action and may be used in combination with an analgesic or with DHE.

Prophylactic treatment. **Migraine** prophylaxis is indicated for patients experiencing more than two attacks per month, or if the severity and the associated symptoms significantly affect the patient's daily life. In active individuals, special consideration must be given to the effect these agents may have on performance and to the effects that exercise may have on the absorption of these agents.

The only agents approved by the US Food and Drug Administration for the prophylactic treatment of **migraine** are propranolol hydrochloride, timolol maleate, methysergide maleate, and divalproex sodium. Propranolol and timolol are nonselective beta blockers and are contraindicated in patients who have asthma, chronic obstructive pulmonary disease, congestive heart failure, or atrioventricular conduction disturbances. These drugs must be used with caution in patients who also take insulin, oral hypoglycemics, or monoamine oxidase (MAO) inhibitors. Other beta blockers may be used, including nadolol. Metoprolol tartrate, a cardioselective beta blocker, may be used in patients who do not tolerate nonselective beta blockers (propranolol, timolol, and nadolol). In many individuals, beta blockers cause a decrease in heart rate and in exercise tolerance. During maximal exercise, these agents may also lower blood pressure and oxygen uptake. The benefits of aerobic exercise may be compromised if pulse measurements are used to determine conditioning; beta blockers will mask an increased pulse rate and patients may overexert.

Methysergide maleate is a vasoconstrictor that inhibits the inflammatory mechanisms of serotonin. Long-term use has been linked to cardiac, pulmonary, and retroperitoneal fibrotic syndromes. Methysergide should never be used for more than 6 consecutive months without a 4- to 6-week hiatus. During methysergide therapy, the patient should be regularly evaluated and an intravenous pyelogram ordered at the end of a 6-month therapeutic interval to rule out retroperitoneal fibrosis. In active individuals, methysergide can cause muscle cramping, weakness, and arthralgias. Divalproex sodium has recently been approved by the FDA for the treatment of **migraine**. It has demonstrated efficacy in patients who have migraines that are refractory to other treatments and those who have concomitant seizure or bipolar disorders.

Other agents are used in **migraine** prevention but have not received FDA approval for this indication. Calcium channel blockers, particularly verapamil hydrochloride and nimodipine, have been effective in **migraine** prophylaxis. Nimodipine has the highest marked selectivity for the cerebral vasculature, but may not be indicated in active individuals because it can cause muscle pain and fatigue. Verapamil hydrochloride is considered effective because of its antiplatelet actions and is not reported to be detrimental to active people.

Clonidine hydrochloride, an alpha-adrenergic blocker, has demonstrated efficacy in **migraine**, particularly in patients who have diet-related attacks.

Antidepressants, including tricyclic agents and MAO inhibitors, have long been recognized as beneficial in **migraine** prophylaxis. Some tricyclics, such as protriptyline hydrochloride, have been linked to resting tachycardia. Active individuals may not be able to tolerate the anticholinergic effects, such as dry mouth, blurred vision, and urine retention. In children with **migraine**, the agent of choice is cyproheptadine hydrochloride, which blocks histamine and serotonin receptors. In adults who have **migraine**, the effects of cyproheptadine have been equivocal.

NSAIDs have demonstrated efficacy in **migraine** prophylaxis. These agents do not affect athletic performance but have been known to cause fatigue as well as gastrointestinal complaints.

Prophylactic treatment for skiers and others who have headaches at higher altitudes may include a diuretic, such as acetazolamide or **furosemide**, or a corticosteroid. The agent should be started immediately before traveling to the higher altitudes. If this procedure does not help, the patient may need to return to a lower altitude.

Freedom for Fitness Pursuits

For active **migraine** patients, it is essential that accurate diagnosis and appropriate therapy be undertaken to maintain the patient's exercise routines. If exertion continues to trigger headaches, neuroradiologic evaluation may be indicated to rule out organic disease. However, the right combination of nondrug and drug therapies usually removes **migraine** as an obstacle to patients' full, active lifestyles.

Table 2. Pharmacologic Treatments for Migraine and Side Effects That May Impair Exercise

Agent	Dose	Route	Effect on Exercise
Abortive			
Sumatriptan succinate*	6 mg, may repeat after 1 hr, up to 12 mg/24 hr	SC	None
Sumatriptan succinate*	25 mg, may repeat in 2 hr, can increase with each attack, up to 100 mg	Oral	None

Ergotamine tartrate*	2 mg, may repeat every 30 min, up to 6 mg/24 hr, 10 mg/wk	Sublingual	None
Ergotamine tartrate with caffeine*	1 mg, 100 mg; may repeat every 30 min, up to 6 tab/24 hr, 10 tab/wk	Oral	Caffeine may act as a stimulant
Ergotamine tartrate with caffeine*	2 mg, 100 mg; may repeat in 1 hr, up to 2 tab/day, 5 tab/wk	Rectal	None
Dihydroergotamine mesylate*	0.5 to 1.5 mg	IM, IV, SC	None
Isometheptene mucate with dichloralphenazone and acetaminophen	65 mg, 100 mg, 325 mg; 2 tabs at onset, may repeat 1 tab every hour up to 5 tab/24 hr	Oral	None
Aspirin	900 mg	Oral	None
Naproxen sodium	825 mg, may repeat 275-550 mg every 30-60 min, up to 1,375 mg/24 hr	Oral	None
Flurbiprofen	50-100 mg, may repeat every 6 hr	Oral	None
Etodolac	300 mg 3 times a day	Oral	None
Mefenamic acid	500 mg	Oral	None
Diclofenac sodium	50-75 mg 2 to 4 times a day	Oral	None
Chlorpromazine	25-50 mg, may repeat	Oral	Sedation

hydrochloride	every 6 hr		
Chlorpromazine	100 mg, may repeat every 6 hr	Rectal	Sedation
Chlorpromazine hydrochloride	25-50 mg, may repeat every 6 hr	IM	Sedation
Prochlorperazine	25-50 mg, may repeat every 6 hr	Oral	Sedation
Prochlorperazine	25 mg, may repeat every 6 hr	Rectal	Sedation
Prochlorperazine	10 mg, may repeat every 6 hr	IM	Sedation

Pain Relieving

Aspirin	500 mg twice a day	Oral	None
Ketoprofen	12.5-25 mg twice a day	Oral	None
Naproxen sodium	275-550 mg twice a day	Oral	None
Ibuprofen	200-400 mg every 4 hr	Oral	None
Ketorolac tromethamine	10 mg 4 times a day	Oral	None
Ketorolac tromethamine	60 mg twice a day	IM	None
Butorphanol tartrate	1 mg, may repeat within 60-90 min; two-dose sequence	Nasal	Possible aberrant psychological profile

	may be repeated every 3-4 hr		
Prophylactic			
Propranolol hydrochloride**	60-160 mg/day	Oral	Mild sedation, bradycardia
Timolol maleate**	10-20 mg/day	Oral	Mild sedation, bradycardia
Nadolol**	20-120 mg/day	Oral	Mild sedation, bradycardia
Metoprolol tartrate	100-200 mg/day	Oral	Mild sedation, bradycardia
Atenolol	25-100 mg/day	Oral	Mild sedation, bradycardia
Verapamil hydrochloride	120-480 mg/day	Oral	Possible bradycardia
Nimodipine	30 mg 3 or 4 times a day	Oral	Possible bradycardia
Nicardipine hydrochloride	20-30 mg 2 or 3 times a day	Oral	Possible bradycardia
Amitriptyline	10-150 mg/day	Oral	Dry mouth
Doxepin hydrochloride	10-150 mg/day	Oral	Dry mouth
Phenelzine sulfate	15-60 mg/day	Oral	None
Aspirin	81 mg/day	Oral	None

Ketoprofen	50-75 mg 2 or 3 times a day	Oral	None
Naproxen	250-750 mg/day	Oral	None
Naproxen sodium	250-750 mg/day	Oral	None
Fenoprofen calcium	600 mg 3 times a day	Oral	None
Flurbiprofen	50-100 mg 3 times a day	Oral	None
Indomethacin	25-50 mg 3 times a day	Oral	None
Piroxicam	20 mg every morning	Oral	None
Nabumetone	500-750 mg twice a day	Oral	None
Diclofenac sodium	50 mg once or twice a day	Oral	None
Clonidine hydrochloride	0.1 mg 3 times a day	Oral	None
Methysergide maleate	2 mg 3 times a day	Oral	None
Divalproex sodium	250-2,000 mg/day	Oral	None

* A 4- to 5-day hiatus must be maintained between days of use to avoid rebound headache.
** Contraindicated in patients who have asthma or chronic bronchitis
SC = subcutaneous, IM = intramuscular, IV = intravenous

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Brain Products for
Headache or **Migraine**

Transformed migraine may be cause of chronic daily headache

Reuters News

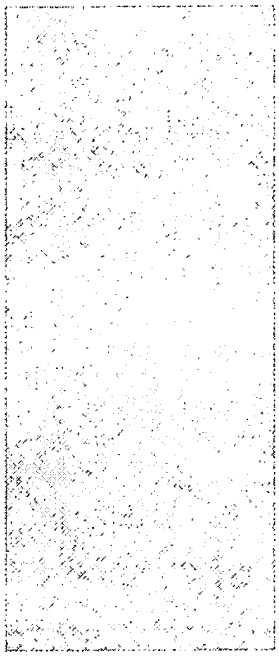
Most patients with chronic daily headache appear to have transformed **migraine**, according to a report in the February issue of Headache.

Individuals with chronic daily headache, characterized by episodes of head pain that occur more than 15 days each month, often have a history of **migraine** with or without aura, or tension-type headache, Dr. John Stirling Meyer of the Baylor College of Medicine in Houston, Texas and co-investigators explain.

Dr. Meyer's group previously noted that patients with intermittent **migraine** have "...excessive cerebral cortical vasodilation after oral **acetazolamide**, which usually precipitated and reproduced their typical headaches."

To further investigate the relationship between these two types of headache, Dr. Meyer's group evaluated 11 patients with chronic daily headache and 12 patients with typical intermittent **migraine**. To this end, they measured cerebral vasodilator capacitance in the subjects at baseline and after administration of oral **acetazolamide**, using CT cerebral blood flow techniques.

Following **acetazolamide**, the increases in local cerebral blood flow in the cortical gray matter of chronic headache patients (11.8%) and migraineurs (16.7%) were comparable. They also found that **acetazolamide** provoked typical **migraine** attacks in 9 patients (82%) with chronic daily headache and in 11 patients with intermittent **migraine** (92%).



Dr. Meyer's group believes that the **acetazolamide**-related provocation of typical **migraine** headache, which was accompanied by local changes in cerebral blood flow, among the chronic headache patients suggests that most of these subjects actually have transformed **migraine**.

Based on these results, they suggest that along with withdrawal of analgesics, caffeine, barbiturates and ergotamines, serotonin agonist drugs may be an effective treatment option for patients with chronic daily headache.

Headache 1999;39:95-100.

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Furosemide inhibits regenerative cortical spreading depression in anaesthetized cats.

Read SJ, Smith MI, Benham CD, Hunter AJ, Parsons AA.

Neurosciences Research, SmithKline Beecham Pharmaceuticals, Harlow, Essex, UK.

Ionic perturbations occur during cortical spreading depression (SD), a phenomenon implicated in migraine pathophysiology. We studied the effect of 0.2, 2 and 20 mg kg-1 i.v. (n=4) furosemide on cortical direct current (d.c.) potential, cerebrovascular laser Doppler flux (rCBF[LDF]), artery diameter and NO concentration in the parietal cortex of the anaesthetized cat during repetitive SD. In vehicle-treated animals (n=4), SD activity was sustained for 50+/-1.8 min. However, duration of SD activity was significantly reduced when compared to vehicle to 39+/-6.6 (n=4), 34+/-8.5 (n=4) and 27.3+/-11.3 min (n=4), at 0.2, 2 and 20 mg kg-1 i.v. furosemide respectively. It is hypothesized that the mechanism of inhibition of SD d.c. activity by furosemide may be through alterations in cortical ion buffering capacity or inhibition of cell swelling in neurones or glia. These mechanisms may represent potential novel drug targets in future migraine therapy.

PMID: 9453270 [PubMed - indexed for MEDLINE]

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Cortical spreading depression in migraine.

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Cortical spreading depression (CSD) is associated with a dramatic failure of brain ion homeostasis as well as efflux of excitatory amino acids from nerve cells and increased energy metabolism. There is strong clinical and experimental evidence to suggest that CSD is involved in the mechanism of migraine. This paper will, based on the experience related to the detection of CSD in humans, discuss pitfalls and possible strategies for detection of CSD in man. Development of reliable methods for detection of CSD in humans will determine the extent to which the large body of experimental findings from animal studies of CSD can be applied to the investigation and treatment of human brain disease. The paper is based on the experience that has been gained from two decades of studies of CSD in relation to clinical neurological diseases.

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J Neurol (2002) 249 : 643 – 645

Cortical spreading depression is linked to pain transmission by the trigeminal nerve

In 1944 the neurophysiologist A. Leao postulated that the visual aura of migraine headaches is related to cortical spreading depression (CSD), an assumption which was based on the observation that the aura drifts across the visual field in accordance with the propagation of CSD. This aura is experienced by approximately 20% of migraine patients, and is characterised by flashing lights and blind spots, which persist for about 30 minutes before the onset of cephalic pain. Nevertheless, the accuracy of Leao's observation was largely ignored in migraine research, because CSD could not be detected in humans at that time. Recent studies using novel technologies in neuroscience, such as blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging and positron emission tomography, have been able to correct this point of view by demonstrating cortical spreading depression within the occipital lobe of migraine patients who experienced visual aura prior to headache development. Leao's suspected relationship between CSD and the visual aura in humans was therefore established.

CSD is characterised by a depolarisation of glia and neurons on the cortical surface, and is associated with a transient increase of cerebral blood flow, transient increases in neurotransmitters (glutamate) and extracellular ions (K^+), as well as dramatic shifts in cortical steady potential (DC). It now represents a key factor in understanding the mechanisms of migraine headaches, but what actually causes the severe pain is unknown to date. The brain is largely insensitive to pain, however the three protective layers of its surface – the outer dura mater, the middle arachnoid and the inner pia mater – form the meninges, a protective region within the cranium which is very sensitive to pain. The meninges are innervated by small-calibre trigeminal axons, which bifurcate near small blood vessels branching from the pial and dural arteries. Moreover, trigeminal innervation is similar for various mammals, such as rats, cats and humans, and their assemblies of neuotransmitters are comparable. For example, experimental stimulation of the large dura and pia matter blood vessels in humans results in migraine-like pain.

Bolay et al. [1], a group of neuroscientists from the Stroke and Neurovascular Regulation Laboratory and the NMR Center, Massachusettes General Hospital, Harvard Medical School in Boston, have taken a giant step forward in unravelling the mechanism of migraine headache by establishing a link between the visual aura and pain by showing that CSD triggers trigeminal afferents in a rat migraine model. In this model, the authors demonstrate that CSD induces blood-flow increase within the pial vessels and the middle meningeal artery (MMA), causes protein leakage in the dura mater, and activates the ipsilateral trigeminal nucleus caudalis. Bolay et al. point out that this mechanism accounts for the increased vasodilation associated with migraine headaches, and links the neurometabolic activity of the brain with the transmission of cephalic pain by the trigeminal nerve. This is a discovery which could lead to a better understanding of the inflammation reaction of the meninges, and the development of anti-inflammatory agents which specifically target cephalic pain.

Meth ds

The Bolay et al. study used a novel technology recently developed by Michael Moskowitz and his colleagues from the NMR Center at Harvard School of Medicine. Dunn et al. [2] designed a method using laser speckle-contrast to image cerebral blood flow. Two-dimentional maps of blood flow within the cerebral cortex, pia vessels and middle meningeal artery (MMA) – exhibiting high spatio-temporal resolution – were obtained. Since speckle contrast is a measure of speckle visibility, blood flow is determined by monitoring the motion of laser scattering particles. To do this, imaging was carried out using a laser diode (780 nm) and CCD camera. Both were positioned above the craniotomy in order to produce an image of 1.75 x 2.5 mm area. The flow of blood was imaged 2 min before CSD induction for a period of one hour. Time-course of blood flow changes was computed at each time-point by pixels with speckle-contrast. Vessel diameter changes were analysed by image-processing software.

Male Sprague-Dawley rats (n = 105; 250–350 g) were anesthetised intraperitoneally with sodium pentobarbital, and the dura mater was opened one hour before CSD induction. A craniotomy was carefully drilled above the middle meningeal artery (MMA) in order to image MMA blood flow. Trigeminal rhizotomy was performed via a ventromedian skull base craniotomy. Cortical steady potential (DC) and electrocorticogram were recorded by single barreled-glass microelectrodes inserted 900 µm into cortex or placed on the surface to prevent CSD induction during electrode insertion. CSD was induced by a pinprick (30 g needle) of the cortex. In this way, triggering of the meningeal afferents was avoided. Multiple CSDs (n = 7) were

evoked for c-fos expression in order to increase the signal-to-noise expression. Immunochemical identification of c-fos was carried out after CSD induction. In order to determine plasma protein leakage in the dura mater, the rats were infused with intravenously with horseradish peroxidase (HRP) at 60 mg/kg to detect plasma protein extravasation.

Results

Bolay et al. pricked the cortical surface of the rats with a pin 7–9 mm away from the MMA. Three minutes later, this traumatic injury produced a large transient (> 2 min) increase in the blood flow of the cortex (250 ± 20% of baseline) and in the pial vessels (205 ± 20% of base line. A wave of changes propagated across the cortical surface of one hemisphere in relation to the neuronal and glial depolarisation. At this early time peak in phase one (P1), there was also a transient increase (127 ± 4% of baseline) in the blood flow within the MMA as the cortical hyperemia spread below the MMA. Subsequent to P1, there was a striking and sustained increase in blood flow occurring within the MMA and its accompaning vein. In this second phase (P2) of MMA blood-flow monitoring, the increase in the flow initiated approx. 5 minutes after CSD was evoked, and reached a peak of 137 ± 5% above baseline at 15 minutes. This sustained increase in blood flow within the MMA lasted approx. 45 minutes. In order to determine whether the increase in MMA blood flow was due to CSD, and not the pinprick, Bolay et al. applied MK-801 (N-methyl-D-aspartate receptor anatogonist) to the cortical pinprick site. MK-801 blocked the propagation of CSD and the neurovascular response, suggesting that CSD caused the increased blood flow in MMA. In addition, the authors detected vasodilation (approx. 10% change in diameter) in the MMA during P1 and P2, suggesting that underlying cortical blood flow did not significantly affect MMA blood flow changes.

In order to determine whether blood flow increase was dependent on trigeminal innervation, Bolay et al. carried out the above experiments after chronic unilateral transection of the trigeminal branch – nasociliary nerve (NCN) – innervating the meninges. This caused an abrogation of the blood flow increase within MMA of P2, but not P1. This means that the P1 rise was not due to trigeminal activation. In addition, the dural blood flow response decreased after sectioning postganglionic parasympathetic fibres projecting from the spenopalatine ganglia in P2, but not in P1. P2 was also reduced following sectioning of the trigeminal root. Acute transection of NCN or parasympathetic efferents produced the same results. The authors conclude that the delayed and sustained blood flow increase in P2 was neurogenically mediated by parasympathetic efferents through brainstem connections.

Bolay et al. assumed that since trigeminal axons projecting into the meninges contain vasoactive neuropeptides which promote plasma protein leakage and vasodilation within the dura mater, this form of neurogenic inflammation should also be observed in the CSD stimulation. The results showed significant protein leakage within the dura mater even after the induction of a single CSD. Edema was prominent around the proximal middle meningeal blood vessels, especially on the ipsilateral side. In addition, chronic NCN transection decreased protein extravasation, and edema formation was suppressed following pre-treatment with L-733,060, a neurokinin-1 receptor blocker. The authors point out this demonstrates the importance of neurogenic mechanisms in edema formation.

The authors investigated the expression of c-fos, a marker of neuronal activity, in order to determine whether second-order neurons in the trigeminal nucleus caudalis (TNC) are activated by CSD. The transcriptional activator protein c-fos is present in very low concentrations in resting cells. Direct activation of the c-fos gene of the target cell by a stimulus triggers the synthesis of c-fos, resulting in high concentrations of the protein within 30–60 minutes. For this reason, the gene c-fos has been designated an immediate early gene. Bolay et al. point out that that the number of c-fos expressing cells is indicator of TNC neuronal activity following noxious stimulation. The results showed that c-fos was expressed mainly in the ventral TNC, the termination site for the ophthalmic trigeminal division. There was also a significantly high expression of c-fos cells in the caudal TNC. C-fos expression was abolished after sectioning of the trigeminal nerve or by treatment with the 5-HT1B/D receptor agonist sumatriptan.

Conclusions

Bolay et al. conclude that their rat model of migraine headache produces evidence suggesting that the cellular, molecular and vascular changes related to cortical spreading depression (CSD) can cause the cephalic pain of aura-induced migraine headaches in humans. This is especially the case when the migraine develops near the trigeminovascular innervation in genetically susceptible individuals. Despite the differences between the rodent and human cortex, Bolay et al. point out that their data establishes a link between CSD and trigeminovascular activation during migraine with visual aura. In other words, CSD acts as a noxious agent within the cerebral cortex to activate trigeminal afferents, thereby triggering the headache associated with middle meningeal vasodilation. The results

of this study are thus in agreement with the observation made by A. Leao in 1944.

Costantino Iadecola [3], the well-known neuroscientist from Cornell University in New York, notes in a review of the Bolay et al. study that an aura does not precede migraine headache in most patients. The aura may be clinically silent in these patients, although there is experimental evidence that meningeal inflammation and aura are not related. He also questions the use of an animal model in this human disease, and whether it can be employed in the development of new therapies. Nevertheless, Iadecola points out that the work of Bolay et al. represents a step forward in understanding the link between visual aura and migraine headache, providing a mechanism by which painless neural events can produce the pain resulting in meningeal inflammation.

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Migraine Headache

1. Migraine Headache
   - one of the most common disorders
   - #1 complaint of individuals consulting neurologists
   - afflicts 10 - 20 % of US population
   - In US, 64 million workdays lost yearly due to migraine
2. Migraine Headache
   - a specific neurological syndrome having a wide variety of symptoms
   - may last for hours or days
   - frequency ranges from 1-2 times/year to 4 times per month
3. Migraine Symptoms
   - basic - throbbing, unilateral headache accompanied by nausea
   - Prodromal (premonition) phase may last for up to 24 hours prior to beginning of the headache
     - consists of changes in mood and appetite
4. Migraine Symptoms
   - photophobia
   - hyperacusia (sensitivity to sound)
   - polyuria
   - diarrhea
   - may be preceded by an "aura"
     - usually a visual alteration
     - may involve sensory or motor changes
5. Migraine Classification
   - Mild
   - Moderate
   - Severe
6. Mild Migraine
   - throbbing headaches, usually unilateral
   - occur mild-moderate pain
   - duration = 4 - 8 hours
   - nausea is common
   - normal activities not impaired
7. Moderate Migraine
   - throbbing headaches, usually unilateral

occur > once/month
moderate-severe pain
duration = 4 - 24 hours
nausea is common
normal activities may be impaired

8. Severe **Migraine**
   throbbing headaches, usually unilateral
   occur >3 times/month
   moderate-severe pain
   duration = > 12 hours
   nausea is common
   normal activities are impaired
9. **Migraine** Headache
   common - **migraine** without aura
   classic - **migraine** with aura
10. Etiology of **Migraine** Headache
    Pathology remains uncertain
    Three theories
        vascular theory
        "**spreading depression** of **cortical** tissue" theory
        "serotonin abnormality" theory
11. Vascular Theory
    postulated in 1940s
    "abnormalities of blood flow appear to play a pivotal role in **migraine** etiology"
    "**migraine** is a vasospastic disorder in which:
        cerebral vasoconstriction produces the prodromal syndrome and
        vasodilation produces the headache
12. Vascular theory has been challenged because
    decrease in cerebral blood flow is not sufficient to produce the neurological symptoms
    increased cerebral BP does not produce pain, edema or focal tenderness associated with migraines
13. "**Spreading depression** of **cortical** activity" theory
    also termed the "**spreading depression** of Leao"
    Spreading depression - a phenomenon observed in mammals that occurs in the cortex in response to a noxious (painful) stimulus
14. "**Spreading depression** of **cortical** activity" theory
    Events following administration of a noxious stimulus at the site:
        focal (localized) reduction of electrical activity
        increased blood flow
    events spread across the **cortical** hemisphere at a rate of 2-3 mm/min.
15. "**Spreading depression** of **cortical** activity" theory
    the EEG of the mammal returns to normal in 10 minutes
    cortical activity may be depressed for 60 minutes
16. "**Spreading depression** of **cortical** activity" theory
    studies of human **migraine** have shown a gradual spread of reduced blood flow (oligemia) which starts in the occipital lobe and advances anteriorly
    blood flow changes do not correlate with location of major cerebral arteries
    blood flow changes are similar to **spreading depression** seen in mammals
17. "**Spreading depression** of **cortical** activity" theory
    the theory states that:

the "aura" of classic **migraine** may occur as a result of the oligemia and **migraine** symptoms result from an evolving process in the cerebral cortex that occurs secondary to:

decreased **cortical** function
decreased **cortical** metabolism
constriction of **cortical** arterioles

18. "**Spreading depression** of **cortical** activity" theory
    Has been challenged because:
    in humans with **migraine**
    regional oligemia is not been observed with common **migraine**, but
    regional oligemia is observed in patients with classic **migraine**
19. Theory of serotonin abnormality
    Serotonin (5-HT) is a neurotransmitter implicated in the etiology of **migraine** headache
    during a **migraine**, plasma and platelet 5-HT levels vary during different phases
    larger than normal amounts are found in urine during most migraines
20. Theory of serotonin abnormality
    migraines may be precipitated by drugs that increase the release of 5-HT, e.g.,
    reserpine
    fenfluramine (Pondamin)
21. Theory of serotonin abnormality
    stimulation of 5-HT-1 receptors is associated with constriction of cerebral blood vessels
    two drugs used to treat **migraine** stimulate 5-HT-1 receptors and inhibit 5-HT release
    ergotamine (Cafergot)
    sumatriptin (Imitrex)
22. Summary - **Migraine** Headache
    Migraine headaches are characterized by changes in cerebral vascular blood flow
    Elevated 5-HT levels are associated with the occurrence of **migraine**
    Drugs which increase 5-HT secretion may precipitate **migraine**
    Drugs which stimulate 5-HT-1 receptors and inhibit the release of 5-HT are beneficial in treating **migraine**

UniSci Daily University Science News

Current Theory About Migraine Headaches Now In Doubt

Migraine is a class of recurrent headache sometimes preceded by an "aura." The aura typically involves visual changes -- seeing lines, spots, or even hallucinations.

Auras have consistently been tied to "**cortical spreading depression**," during which a wave of decreased brain cell activity crosses the cortex, the outermost part of the brain. This presumed connection contributed to the theory that **cortical depression** could spark the aura and, subsequently, the pain of **migraine**.

But a number of clinical and experimental observations conflict with this theory, especially the evidence that only one in five **migraine** patients experiences an aura preceding the pain and other symptoms (e.g., difficulty with speech or movement, tingling sensations, or vertigo).

This makes the dominant contemporary theory seeking to explain **migraine** headaches unlikely to be correct, say the researchers of a report published in the January 2001 issue of *Annals of Neurology*, the scientific journal of the American Neurological Association.

The German researchers, working in an animal model, failed to find a link between the wave of brain activity known as **cortical spreading depression**, postulated to underlie **migraine** symptoms, and various markers of the inflammation that accompanies **migraine** headache pain.

"We suspect that a still-unidentified stimulus causes **spreading depression** on the one hand and headache pain on the other," said senior author Frank Richter, Ph.D., a researcher at the University of Jena in Germany.

Dr. Richter and his colleagues decided to test the theory by triggering **spreading depression** in the cortex of rats and then probing for activity in the nervous system and blood circulation that would reflect the

instigation of migraine headache.

What they discovered cast even further doubt on the presently accepted theory.

The researchers found no change in the activity of nerve centers that should have been the "output station" if spreading depression causes an inflammation in the dura mater, a membrane that covers the brain.

The dura mater becomes inflamed during migraine in humans.

The researchers also failed to detect evidence of spreading depression-induced dura mater inflammation; in particular, they found no increases in the chemicals calcitonin gene-related peptide (CGRP) and prostaglandin E-2, which typically increase in concentration during migraine headaches.

"Absence of CGRP release is a pivotal negative finding, because it is a reliable finding in migraine patients during headache that can link human and experimental studies," wrote Peter J. Goadsby, MD, PhD, of the National Hospital Institute of Neurology in London, in an accompanying editorial.

Richter and his colleagues believe that the best explanation for the observed anomaly is that cortical spreading depression is a process parallel to, but detached from, the phenomenon that causes the pain of migraine. The researchers emphasize that further research must be conducted before changes in the conventional treatment for migraine headaches can occur.

"Our data will not influence current migraine therapy," says Richter. Instead, the researchers will now focus on finding the common source of the pain processes in the dura and the spreading depression and aura.

31-Jan-2001

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The British Journal of Psychiatry (2003) 182: 428-433

Depersonalisation disorder: clinical features of 204 cases

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Declaration of interest None.

Background Depersonalisation disorder is a poorly understood and underresearched syndrome.

Aims To carry out a large and comprehensive clinical and psychopathological survey of a series of patients who made contact with a research clinic.

Method A total of 204 consecutive eligible referrals were included: 124 had a full psychiatric examination using items of the Present State Examination to define depersonalisation/derealisation and 80 had either a telephone interview (n=22) or filled out a number of self-report questionnaires. Cases assessed were diagnosed according to DSM—IV criteria.

Results The mean age of onset was 22.8 years; early onset was associated with greater severity. There was a slight male preponderance. The disorder tended to be chronic and persistent. Seventy-one per cent met DSM—IV criteria for primary depersonalisation disorder. Depersonalisation symptom scores correlated with both anxiety and depression and a past history of these disorders was commonly reported. 'Dissociative amnesia' was not prominent.

Conclusions Depersonalisation disorder is a recognisable clinical entity but appears to have significant comorbidity with anxiety and depression. Research into its aetiology and treatment is warranted.

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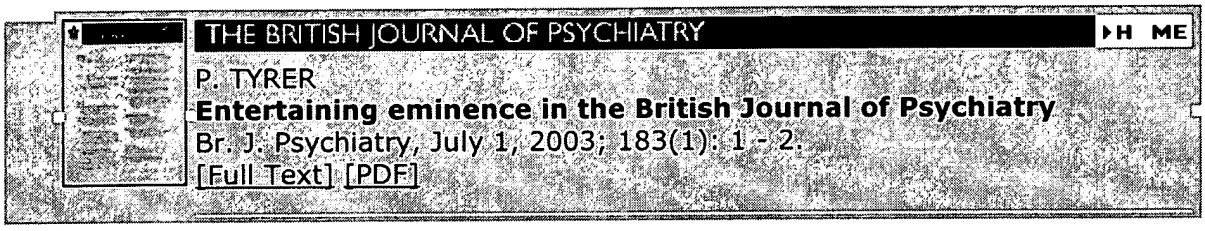

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Depersonalisation in migraine.

C. Majella Cahill

BJP Online, 20 Jun 2003 [Full text]

Headache Cybertext/Migraine aura status

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Migraine diagnosis

Terminology

***Migraine** aura status* is not included among the sub-types of **migraine** listed in the 1988 classification of **migraine** by the International Headache Society (IHS), probably because the committee members were unaware of this condition. They did, however, list a class called ***migraine** with prolonged aura*. To be placed into this class, at least one of the patient's aura symptoms must last more than 60 minutes and less than 7 days.

In my 1982 report of two patients, I used the term *Prolonged **migraine** aura status*.

Subsequent articles have used the following terms:

1. Sustained visual aura
2. Persistent positive visual phenomena
3. Persistent **migraine** aura

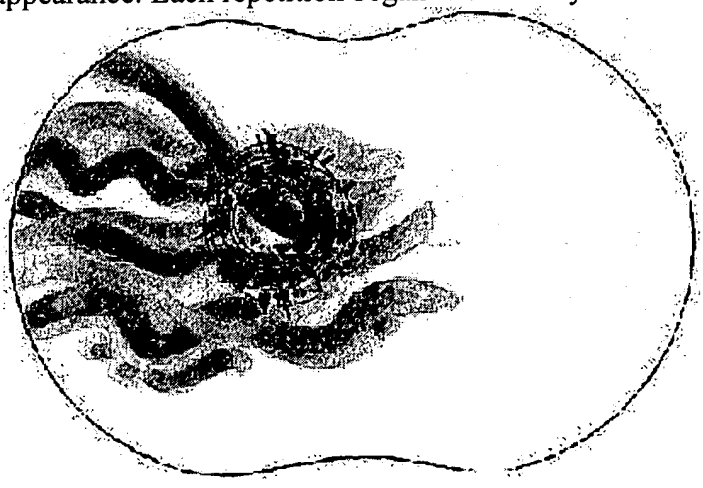
What are the symptoms?

The symptoms are those of a migrainous visual aura that either recurs repetitively hour-after-hour, day-after-day for weeks, months, or years, or does not abate for weeks, months, or years. Aura symptoms other than visual may be a part of the picture, but so far no one has reported a **migraine** aura status composed soley of non-visual aura symptoms.

Examples (abbreviated) from the medical literature

Repetitive variety

Patient 1 of Haas, 1982: This 70-year-old man had stereotyped repetitive attacks several times per hour for about 5 weeks. His description of them is enhanced by his painted rendition of their appearance. Each repetition began with slowly undulating thick gray lines, which changed in a few minutes into a pinwheel of bright whirling color in his left visual field. Several minutes later this image slowed down and disappeared. After more than a week of suffering these hallucinations, he also developed brief attacks of "electrical" paresthesias in his left hand. These were less frequent than the visual phenomena and alternated with them irregularly. Throughout his ordeal, he had a dull headache over his right eye.



The 7 patients with "aura status" reported by Haan et al. 2000

The 7 patients with "aura status" reported by Haan et al., 2000 experienced several mostly visual auras daily for weeks, very often without headache. They were asymptomatic between the auras.

Continuous variety

Case of Luda et al., 1991: This 65-year-old woman developed "scintillating scotomas" in her right visual field without headache on May 3, 1990 and they were still present and unremitting when the authors reported her problem over 12 months later. The hallucination was described as "scintillating geometrical figures (in the shape of either rings or chains)..."

Patient 3 of Liu et al., 1995: On November 10, 1992, this 29-year-old woman "experienced sudden disorientation followed by stars filling the visual field of both eyes, followed by a diffuse, nonpulsating headache. When the headache ceased, she was left with "constant flashing lights and circles which were worse at night..." These visual symptoms resolved spontaneously in April 1993. Months later, she experienced "zig-zag" lines for 10 minutes followed by a pulsating headache. She also had brief attacks of unilateral paresthesias sometimes followed by headaches both before and after the persistent aura.

Patient 1 of Chen et al., 2001: This 45-year-old woman reported seeing an occasionally flickering coin-sized white spot in her left field of view for 3 months. It began "after" a **migraine** headache without aura. It prevented reading.

Patient 2 of Chen et al., 2001: This 24-year-old woman complained of seeing numerous stars persistently flickering in her right visual field for 3 years. At times they formed a single light. This phenomenon developed during a **migraine** attack. She had suffered migraines from childhood. A visual aura of of bright yellow flickering stars lasting 30-60 seconds had occurred during most of her **migraine** headaches.

Patient of Spierings, 2002: This 41-year-old man with **migraine** with typical visual aura from childhood developed his typical aura while upset in October 1996. It was unusually vivid and was accompanied this time by tingling in his left upper limb for 30 minutes. This was followed by severe headache with photophobia, generalized weakness, and confusion. The visual disturbance never disappeared, but has persisted to the time of Spiering's report. The patient sees things as though looking through a veil, and "bright-white, flickering, zigzag lines in the periphery of both visual fields" (his typical aura) come and go.

Continuous, strongly fluctuating variety

Patient 1 of Rothrock, 1997: Two months before she was seen by the author, this 61-year-old woman experienced a particularly severe prolonged **migraine** with "jagged zigzags like crushed broken glass" to the left of a scotoma in her left visual field. This hallucination persisted after the headache ceased. It had been fluctuating in size

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persisted after the headache ceased. It had been fluctuating in size, without disappearing entirely. In addition, she had developed similarly fluctuating but persistent numbness and tingling in the left face and lips.

Who gets these phenomena?

They can occur from childhood to old age. All reported patients had previously experienced either **migraine** headaches with visual auras, **migraine** visual auras without headache, or **migraine** headaches without auras, or various combinations of these **migraine** varieties.

What have brain tests--MRIs, EEGs, and SPECT scans--told us?

CT and MRI have not shown notable abnormalities. Thus, cerebral infarctions and tumors are well-excluded causes. EEGs on 21 patients showed abnormalities in only two, a father and daughter with occipital slow waves. So, the EEG evidence excludes an epileptic cause. SPECT scans have shown decreased cerebral perfusion in most of the patients scanned, and in those with phenomena in just one hemifield the decreases have been on the side opposite the perceptions (e.g. left field phenomena, right cerebral perfusion decrease). In some scans the perfusion decreases have been limited to the occipital lobe. These findings suggest that the affected cerebral regions are metabolically depressed, and they are compatible with the data from more quantitative tests in patients with typical migrainous auras.

Treatment

Patient number 1 reported by Haas in 1982 (see above) had his frequent repetitive visual attacks fade away quickly 2 days after he began taking cyproheptadine and after he failed to improve on acetylsalicylic acid. Three of the 7 patients of Haan et al., 2000 (see above) with repetitive attacks similar to those of Haas were treated with acetazolamide (250 mg twice or thrice daily) and all 3 experienced cessation of their auras in a matter of days. When the drug was discontinued or its dosage was lowered, the auras returned. None of their 7 patients responded to valproate or propranolol.

Rothrock (1997) reported the disappearance of persistent auras during treatment with divalproex in 2 patients, and Chen et al. (2001) reported the disappearance of persistent auras during treatment with lamotrigine in 2 patients. A host of other drugs have been unsuccessful, including phenytoin, phenobarbital, carbamezepine, acetylsalicylic acid, inbuprofen, verapamil, nifedipine, nimodipine, flunarazine, amitriptyline, clonazepam, fluoxetine, sertraline, baclofen, and buspirone. However, topiramate (Topamax) may be

effective for some patients, as indicated in the following e-mail message I received on June 14, 2002:

> **"I've suffered fr m Migrain Aura Status (alth ugh I didn't kn w to call it ther than just Migrain) f r approximately 2 1/2 years. I'v been treated quit successfully for this with Topamax. I b gan taking 50mg twice a day in January 2001 and within a couple of weeks the visual phenomenon cleared up. This spring we decreased the dosage to 25mg in the morning & kept the night dosage at 50mg and within a week the visual symptoms began to return. I also experienced a migraine headache during this time. Needless to say, I'm back to the original dose and the symptoms have subsided."**

Two continuous, prolonged migrainous visual auras, of 11 and 5 days duration were reported by Rozen, in September, 2000, to disappear within a few hours after an intravenous dose of 20 mg of **furosemide**. This drug was chosen, because it has been shown to inhibit the generation and duration of cortical spreading depression (the putative physiological cause of migrainous auras) induced by potassium in the cat. Although these two patients did not have ***migraine*** *aura status* as discussed above, perhaps they would have if left untreated.

The evidence so far suggests that acetazolamide may be the premier drug for patients with the repetitive form of aura status, and that divalproex (valproate), lamotrigine, or topiramate should be first choices for patients with the continuous form. When these oral drugs are ineffective, an intravenous injection or injections of **furosemide** should be tried.

Comment

I have grouped both the repetitive and continuous forms of the prolonged visual migrainous auras under the rubric of **migraine aura status** since they both share the characterizing feature of affecting persons for weeks, months, or longer. Since the word "status" as used in "status epilepticus" means a prolonged condition, whether the seizures are repetitive or unremitting, its use for both of the prolonged aura states seems appropriate. Further studies might tell us whether these two aura states are basically the same condition or not.

1: Neurology. 2000 Nov 28;55(10):1588-9. Related Articles, Links

Acetazolamide treatment for migraine aura status.

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Glossar: A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

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Die Behandlung der Migräneattacke

In der **Therapie der Migräne** spielt der Placebofaktor bekanntlich eine beträchtliche Rolle und wird von vielen Autoren nahezu übereinstimmend in einer Größenordnung von etwa 40% eingeschätzt. (Diener HC, Brune K, Gerber WD, Göbel H, Pfaffenrath, V. Behandlung der Migräneattacke und Migräneprophylaxe. Empfehlungen der Deutschen Migräne- und Kopfschmerzgesellschaft. Nervenheilkunde 1997; 16: 500-10.) Erfolgskriterien für eine erfolgreiche Behandlung einer Migräneattacke ist eine Besserung der Kopfschmerzen von schwer oder mittelschwer auf leicht oder Kopfschmerzfrei innerhalb zwei Stunden nach Applikation des entsprechenden Präparates und eine reproduzierbare Wirkung bei 2 von 3 Migräneattacken.

Bei leichten bis mittelschweren Attacken: Kombination von Antiemetika also Medikamenten gegen Übelkeit (z. B. Metoclopramid 10–20 mg als Supp. oder p. o., z. B. Paspertin®, bzw. Domperidon 10 mg p. o., z. B. Motilium®) mit 1000–1500 mg Acetylsalizylsäure (als Brause- oder Kautablette), oder Paracetamol 1000mg, alternativ 400–800 mg Ibuprofen oder 250 mg Naproxen. Ausweichmedikation: 500–1000 mg Metamizol p. o. Die Vorbehandlung mit einem Antiemtikum wie Metoclopramid oder Domperidon ist nötig, um die im Migräneanfall erlahmte Magen- und Darmbeweglichkeit anzuregen und damit die Aufnahme des Schmerzmittels aus dem Darm zu fördern.

Die Kombination der ersten Wahl bei leichten bis mittelschweren Migräne Attacken:	
Wirksamkeit nur bei frühzeitiger Einnahme	
Medikament gegen Übelkeit (auch wenn keine empfunden wird)	**Metoclopramid 10–20 mg als Supp. oder p. o., z. B. Paspertin®, bzw. Domperidon 10 mg p. o., z. B. Motilium®**
Einfaches Analgetikum kein Mischpräparat, ausreichende Dosis	**1000–1500 mg Acetylsalizylsäure (als Brause- oder Kautablette), oder Paracetamol 1000mg, alternativ 400–800 mg Ibuprofen oder 250 mg Naproxen.**

Migränemittel zur Einnahme bei der Attacke mit typischer Dosierung (Beispiele) (Keine Haftung, informieren Sie sich bei dem Arzt der Sie und ihre gesundheitlichen Probleme kennt über das für Sie geeignete Medikament und Ihre speziellen Risiken.)	Paracetamol + Metoclopramid	500 -1000 mg + 30 mg M. (absolutes Maximum 3000mg Paracetamol/Tag bei einem gesunden Erwachsenen)
	Ibuprofen	400 -1200 mg
	ASS + Metoclopramid	1000 mg +10 mg (Vorsicht Aspirin ist für Asthmatiker, Kinder und Magenempfindliche nicht geeignet.)
	Naproxen	750 mg
	Diclofenac	50 mg
	Sumatriptan	25-100 mg Vorsicht bei vorheriger Ergotamin-Einnahme verboten, Vorsicht bei Herzkrankheiten.
Warum Ergotamine heute nicht mehr oder nur noch sehr selten und überwacht	**Die neuen Triptane sind besser verträglich aber:**	

eingesetzt werden:. Bei der Therapie mit Ergotalkaloiden war größte Vorsicht geboten! Die zu häufige Einnahme von Ergotalkaloiden konnte sehr schnell die Migräneattacken in ihrer Häufigkeit und Intensität verschlimmern! Sehr leicht konnte ein ständiger, täglicher Kopfschmerz entstehen, ein sogenannter medikamenteninduzierter Dauerkopfschmerz. Bei Absetzen entsteht ein sogenannter Entzugskopfschmerz und die Betroffenen müssen deshalb ständig weiter und mit der Zeit mehr und mehr Ergotalkaloide einnehmen, um nicht einen Entzugskopfschmerz zu erleiden. Bei Dauertherapie konnten auch sehr schwere Durchblutungsstörungen in den verschiedenen Körperorganen auftreten, meist zunächst in den Armen und Beinen. Die Durchblutungsstörungen konnten sogar sehr ernste Folgen haben, bis hin zum tödlichen Verlauf mit Herzinfarkt oder Absterben von Teilen des Darmes aufgrund mangelnder Durchblutung, weil eine dauernde Gefäßverengung verursacht wurde. Nach : Forschungsergebnisse der Deutschen Migräne- und Kopfschmerzgesellschaft Ergotamine und Triptane — pro und contra *Prof. Dr.med. Hartmut Göbel*	·sie dürfen nicht eingesetzt werden wenn- keine ausreichende ärztliche Voruntersuchung einschließlich Blutdruckmessung und Elektrokardiogramm, sowie individueller Beratung vorgenommen wurde. Dies gilt auch gerade für den erstmaligen Einsatz in der Notfallsituation bei schweren Migräneattacken. -andere Therapiemöglichkeiten zur Vorbeugung und Akutbehandlung von Migräneattacken noch nicht systematisch, individuell ausprobiert worden sind. -ein medikamenteninduzierter Dauerkopfschmerz besteht. Das Risiko eines medikamenteninduzierten Dauerkopfschmerzes ist bei Triptanen größer als bei normalen Schmerzmitteln -Gegenanzeigen bestehen, wie zum Beispiel ein Zustand nach Herzinfarkt, Zustand nach Schlaganfall, andere Gefäßerkrankungen, Bluthochdruck, Leber- oder Nierenerkrankungen Nach : Forschungsergebnisse der Deutschen Migräne- und Kopfschmerzgesellschaft Ergotamine und Triptane — pro und contra *Prof. Dr.med. Hartmut Göbel*
zurück zum Seitenanfang	

Auch **Rezeptfreie Kopfschmerztabletten können schwerste Nebenwirkungen haben,** sie sollten gerade bei den Arzneimitteln, die Sie selbst frei kaufen können den Beipackzettel besonders sorgfältig lesen und wie es die Werbung empfiehlt Ihren Arzt fragen. Wer weiß schon, dass Aspirin Asthmaanfälle auslösen kann oder bei Kindern eine lebensgefährliche Hautkrankheit auslösen kann. Paracetamol kann bei Überdosierung eine akutes Leberversagen auslösen.....

UAW Aspirin: Magen-Darm-Trakt: Übelkeit, Erbrechen, Schmerzen, Ulzera, Blutungen; Analgetika-Intoleranz (Rhinitis, Bronchospasmus), insbes. bei Patienten mit Asthma, Nasenpolypen; Urtikaria, Leber- und Nierenfunktionsstörungen

IA Aspirin: Erhöhtes Blutungsrisiko mit Antikoagulanzien, erhöhte Gefahr von Magen-Darm-Ulzera mit Glucocorticosteroiden, Wirkungsabschwächung von Antihypertensiva/ Diuretika, Toxizitätserhöhung von Methotrexat, Wirkungsverminderung von Probenecid, Sulfinpyrazon,

.... **Wichtig ist also auch hier vorher Ihr spezielles Nebenwirkungsrisiko abzuschätzen und das Medikament hiernach auszuwählen.**

Risikoprofil für Magenblutungen (Wann besonderer Magenschutz besonders bei Älteren)
Aspirin oder nichtsteroidalen Antirheumatika sind für über 80 Prozent aller Ulkusblutungen des älteren Menschen verantwortlich.
Andere Risikofaktoren
orale Antikoagulantien
Ulkusanamnese
Herzinsuffizienz
orale Corticosteroide
Diabetes mellitus
Raucheranamnese
Weil 5, Langmann MJS, Wainwright P et al.: Peptic ulcer bleeding: accessory risk, factors and interactions with non-steroid atiinflammatory drugs. Gut 2000; 46:*[Abstract]*.
Zu den Nebenwirkungen von Ass siehe auch: *The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke.N Engl J Med. 1991;325:1261-1266.MEDLINE und UK-TIA Study Group.The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results.J Neurol Neurosurg Psychiatry.1991;54:1044-1054.MEDLINE*

"Endlich Migräne-Stopper da!" ***Es ist kein wesentlich anderer Effekt als mit bisherigem Acetylsalizylsäure -Präparaten zu erwarten.*** In der Aspirin®Migräne Studie mit 374 Migräne-Patienten, wurde bestätigt, dass Acetylsalicylsäure (ASS) in einer magenfreundlichen Brauseformulierung bei Migräne-Kopfschmerz wirksamer ist als Placebo. Obwohl kein Antiemetikum gegeben wurde, sprachen 55 Prozent der Patienten auf die Therapie mit zwei Tabletten Aspirin® Migräne mit je 500 Milligramm ASS an. Auf Placebo haben mit 36,8 Prozent signifikant weniger angesprochen. Als Therapie-Erfolg galt: Rückgang der Kopfschmerzen vom Schweregrad stark oder mäßig stark auf leichte oder keine Schmerzen zwei Stunden nach Präparat-Einnahme. Nebeneffekte wie Übelkeit, Erbrechen oder Licht- und Lärmempfindlichkeit seien zum Teil um mehr als 50 Prozent reduziert worden. "

Kombinationspräparate wie die Dreierkombination aus ASS, Paracetamol und Koffein (Thomapyrin®) sind möglicherweise besser als ihr Ruf. es ist inzwischen umstritten, ob sie häufiger als Monopräparate zu Abhängigkeit (Analgetika induzierten Kopfschmerzen) führen. (US-Headache Consortium 7/2000ein von der US-amerikanischen neurologischen Gesellschaft zusammengestelltes interdisziplinäres Gremium. In dieses Gremium sind Experten aus sieben medizinischen Organisationen, zum Beispiel aus der American Headache Society und der National

Headache Foundation berufen worden. Große Studien sind allerdings noch im Gange endgültige Ergebnisse werden erst in 2 Jahren vorliegen.). **Bis dahin und dennoch gilt bisher möglichst keine Kombinationspräparate.**

—Bei schweren Migräneattacken oder bei Versagen dieser Therapieoptionen:

(Nur bei sieben Prozent der Migräne-Attacken sind Triptane notwendig.)

Behandlung mit den sog. Triptanen, die neben der Hemmung der neurovaskulären Entzündung auch eine vasokonstriktorische Wirkung haben. Zur Zeit sind mit Sumatriptan (Imigran®), Naratriptan (Naramig®), Zolmitriptan (AscoTop®) und Rizatriptan (Maxalt®) vier Triptane im Handel; im nächsten Jahr soll noch Eletriptan dazukommen. Hauptproblem der Triptane ist neben dem hohen Preis häufig das Wiederauftreten der Kopfschmerzen (im Durchschnitt zwischen 20 und 40% der Patienten) nach zwölf bis 24 Stunden. Daneben gelten für die Triptane einige Kontraindikationen wie Co-Medikation mit Ergotaminen, koronare Herzkrankheit, Herzinfarktanamnese, Herzrhythmusstörungen, schwere Leber- und Niereninsuffizienz sowie schwere unbehandelte arterielle Hypertonie. Im Vergleich zwischen 10 mg Rizatriptan und 50 mg Sumatriptan zeigen sich eine etwas raschere Wirkung und eine etwas bessere Wirkung von Rizatriptan im Verhältnis zu Sumatriptan. Bei den Nebenwirkungen bestehen lediglich geringe Unterschiede. Da Rizatriptan seltener zu einem Engegefühl im Bereich der Brust führt, sollte es Patienten gegeben werden, die unter diesen Nebenwirkungen nach Sumatriptan leiden. Rizatriptan hat eine höhere Durchgängigkeit durch die Blut-Hirn-Schranke, was erklärt, warum es häufiger zu Müdigkeit und unsystematischem Schwindel führt. (Goldstein J, Ryan R, Jian K, et al., and the Rizatriptan Protocol 046 Study Group. Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Headache 1998;38:737-47.) Naratriptan ist als einziges Triptan weniger wirksam als die anderen Triptane und hat auch einen langsameren Wirkungseintritt (Goadsby PJ. A triptan too far? J Neurol Neurosurg Psychiatry 1998;64:143-7.). Bei Prophylaxe mit einem Betablocker sollte die halbe Dosis der Triptane gegeben werden.

Sie dürfen das Triptan nicht schon nehmen, wenn sie die ersten Anzeichen einer Migräne zu verspüren glauben (im Gegensatz zur Einnahme von normalen Schmerzmitteln) und auch nicht bei einer beginnenden Aura. Eine solche prophylaktische Einnahme zählt zu den häufigen Fehlern der Migränetherapie, und damit wird die Wirkung der Triptane verspielt. Erst wenn die Migräneattacke sicher beginnt, ist das Triptan am Platz. Eine zu späte Einnahme beeinträchtigt ebenfalls die Wirkung. Der Patient muss also den optimalen Einnahmezeitpunkt herausfinden. Dies gelingt meist nach zwei bis drei Attacken.

Wenn einfache Schmerzmittel mit Antiemetikum nicht ausreichen.

Substanz	Dosis	Nebenwirkungen	Kontraindikationen	Besonderheit
Sumatriptan (Imigran®)	25 - 100 mg 25 - 100 mg p.o. 6 mg s.c. 25 mg Supp 10 - 20 mg nasal	Druck-, Wärme-, Schwere-Druck-, Wärme-,Schweregefühl, "Brustschmerzen", Kältegefühl, Lokalreaktion an der Injektionsstelle, Atemnot, allgemeines Schwächegefühl	Hypertonie, KHK, Angina Hypertonie, KHK, Angina pectoris, Myokardinfarkt, M. Raynaud, AVK, Schwangerschaft, Stillzeit, <18 und >65 J. Prophylaxe mit DHE oder Methysergid, Ergotaminmißbrauch, Migräneaura **(Kein Patient sollte sowohl**	

			Ergotamine als auch Triptane im Arzneischrank haben)	
Zolmitriptan (Ascotop®)	2,5 - 5 mg p.o.	Schwindel, Benommenheit Wärmegefühl, Schwäche, Mundtrockenheit, Schweregefühl, "Brustschmerzen", Engegefühl im Hals	wie Sumatriptan WPW-Syndrom	Lipophil und damit ZNS-gängig, spezifischer als Sumatriptan ($5\text{-}HT_{1B}$ und $5\text{-}HT_{1D}$ Rezeptoren)
Naratriptan (Naramig®)	2,5 - 5 mg p.o.	Müdigkeit, Parästhesien, Engegefühl der Brust	wie Zolmitriptan	lange Halbwertszeit und damit lange Wirksamkeit-Wiederkehren der Kopfschmerzen innerhalb der Attacke am seltensten, seltener Nebenwirkungen, aber auch etwas weniger wirksam als Sumatriptan
Rizatriptan (Maxalt®)	5 - 10 mg p.o. bzw. Maxalt lingual	wie Sumatriptan	wie Sumatriptan; bei Propanolol-Medikation nur 5 mg Rizatriptan	höhere Wirksamkeit, schnellerer Wirkungseintritt, als Sumatriptan
Eletriptan (Relpax®)		wie Sumatriptan	noch nicht zugelassen	soll am wirksamsten sein, aber auch am häufigsten Nebenwirkungen haben.
	Nach:	Gibt es eine differentielle Indikation für Triptane bei der Migräneattacke?	Volker Pfaffenrath	

Pharmakokinetik der Triptane für die Behandlung schwerer Migräne A

Drug	Zufuhr	Wirkungseintritt (nach Minuten)	Wirkungsmaximum (nach Minuten)	Bioverfügbarkeit (%)	Dosis (mg)	Maximal Dosis (mg)	S n S V P
Sumatriptan (Imigran®)	subcutan Spritze	15	12	97	6	12	
Sumatriptan (Imigran®)	Nasenspray	15-20	60-90	17	5 bis 20	40	
Sumatriptan (Imigran®)	Tablette	30-90	150	15	25 bis 100	200	
Zolmitriptan (Ascotop®)	Tablette	60	120	40	1.25 bis 5	10	
Naratriptan (Naramig®)	Tablette	60-180	180-240	70	1 bis 2.5	5	
Rizatriptan (Maxalt®)	Tablette	30-120	60-90	45	5 bis 10	30	
Almotriptan (Almogran®)	Tablette	60-180	90-240	70	6.25 bis 12.5	2	
Frovatriptan (Allegro®)	Tablette	120	120-240	20	2.5 bis 5	7.5	
Eletriptan (Relpax®)	Tablette	60	60	50	40	160	

Modifiziert nach Marcus Ferrone, B.S., M.S., Pharm.D. cand. Susannah E. Motl, Pharm.D Current **Current Pharmacotherapy for the Treatment of Migraine** U.S. Pharmacist, *March 2003,* Ferrari MD. The war of the triptans. In: EFNS Conference; 1999; Lisabon; 1999.Diener et al. Therapie der Migräneattacke und Migräneprophylaxe, Empfehlungen der **Deutschen Migräne- und Kopfschmerzgesellschaft**

Kontraindikationen für Triptane: Hypertonie, koronare Herzerkrankung, Angina pectoris, Myokardin M. Raynaud, arterielle Verschlußkrankheit der Beine, TIA oder Schlaganfall, Schwangerschaft, Stillzeit, schwere Leber- oder Niereninsuffizienz, multiple vaskuläre Risikofaktoren

wichtigste Nebenwirkungen der Triptane: Engegefühl im Bereich der Brust und des Halses, Parästhes Kältegefühl, Lokalreaktion an der Injektionsstelle, erhöhtes Risiko medikamenten- induzierter Kopfschr

Die Behandlungsstrategien für Migräne werden sich möglicherweise ändern.

Mindestens 3 Behandlungsstrategien werden bisher für akute Migräneattacken vorgeschlagen: stufenweise Behandlung von einer Attacke zur nächsten mit steigernder analgetischer Potenz, stufenweise Behandlung innerhalb einer Attacke mit steigernder analgetischer Potenz, und eine von vornherein an den Schweregrad angepasste Therapie.

Die Ergebnisse einer neuen internationalen Studie mit 835 Migränepatienten sprechen für eine von Anfang an besser angepasste Behandlung. In der Studie wurden 3 Behandlungsverfahren für jeweils 6 Migräneattacken pro Patient verglichen.

Bei stufenweise Behandlung von einer Attacke zur nächsten fangen die Patienten mit nicht spezifischer Therapie an (einfaches oder Kombinationsanalgetikum wie Aspirin oder Paracetamol). Falls bei mehreren Attacken dies zu unbefriedigenden Ergebnissen führt, geht er wieder zum Arzt und es wird eine Steigerung zu einem wirksameren Schmerzmittel oder Vorgehen besprochen. Dieser Prozess wird wiederholt bis sich befriedigende Ergebnisse einstellen. Dieses Konzept wird bisher in den meisten Behandlungsrichtlinien empfohlen. Es hat Vor- und Nachteile.

Bei der stufenweisen Behandlung innerhalb einer Attacke mit steigernder analgetischer Potenz und Spezifität wird zunächst während der Attacke mit einem einfachen Analgetikum angefangen. Es wird besprochen, dass wenn dieses nach einer festgelegten Zeit (meist 2 Stunden) nicht wirkt zur nächsten Stufe übergegangen wird- meist spezifischen Migränemedikamenten. Bei dieser Strategie haben die Patienten von vorneherein eine Handhabe für einen unzureichenden Behandlungserfolg.

Bei von vornherein an den Schweregrad angepasster Therapie wird bereits bei der ersten Einnahme je nach Schweregrad aus der gesamten Palette selektiert.

In einer neuen Studie wurden die 3 Verfahren verglichen.

bei an den Schweregrad angepasster Therapie erhielten die Patienten
mit Grad II Kopfschmerzen Aspirin, 800 bis 1000 mg (je nach Land), plus Metoclopramid, 10 mg, als Akutbehandlung für die Migräneattacken. Bei Grad III oder IV Kopfschmerzen erhielten sie Zolmitriptan, 2,5 mg, als sofortige Akutbehandlung.

Bei stufenweise Behandlung von einer Attacke zur nächsten
behandelten die Patienten ihre Kopfschmerzen während der ersten 3 Attacken mit Aspirin, 800 bis 1000 mg (je nach Land), plus Metoclopramid, 10 mg . Die die keinen befriedigenden Behandlungserfolg erzielten wurden angewiesen zu nächsten Schritt Zolmitriptan, 2,5 mg, als sofortige Akutbehandlung für die nächsten Attacken überzugehen. Die anderen sollten bei Aspirin und Metoclopramid bleiben.

Bei der stufenweisen Behandlung innerhalb einer Attacke
behandelten die Patienten ihre Kopfschmerzen zunächst mit Aspirin, 800 bis 1000 mg (je nach Land), plus Metoclopramid, 10 mg . Die die nach 2 Stunden keinen befriedigenden Behandlungserfolg erzielten wurden angewiesen zu nächsten Schritt Zolmitriptan, 2,5 mg, zusätzlich einzunehmen. . Die anderen sollten bei Aspirin und Metoclopramid bleiben.

Resultat der Studie: Der Erfolg bei von vorneherein **bei an den Schweregrad angepasster Therapie war nach 2 Stunden (wie eigentlich zu erwarten)** signifikant besser,(52.7%) gegenüber den beiden anderen Gruppen (40.6%; $P<.001$) oder (36.4%; $P<.001$). Die Ausfallzeiten waren ebenfalls bei diesen 6 Attacken in dieser Gruppe signifikant geringer.

Allerdings waren auch die Nebenwirkungen signifikant häufiger (321 Ereignisse) gegenüber (159 oder 217 in den beiden anderen Gruppen), die meisten Nebenwirkungen wurden als mild bis mäßig in ihrer Intensität beschrieben.

Eine von vorneherein an den Schweregrad angepasste Therapie erwies sich damit den anderen Verfahren als überlegen. Kommentar der DKMG: Die Tatsache, dass in Deutschland in der Regel die Stufentherapie benutzt wird, beruht darauf, dass ein Arzneimittelbudget besteht und bei der häufigen Verschreibung von Triptanen der Nachweis geführt werden muss, dass die Patienten auf eine Behandlung mit Analgetika in Kombination mit Metoclopramid nicht angesprochen haben.

Hinweis statt Zolmitriptan sind sicherlich auch alle anderen Triptane ähnlich verwendbar.

Stratified Care vs Step Care Strategies for Migraine The Disability in Strategies of Care (DISC) Study: **A Randomized Trial** *Richard B. Lipton, MD; Walter F. Stewart, PhD, MPH; Andrew M. Stone, MSc; Miguel J. A. Láinez, MD; James P. C. Sawyer, MB, ChB JAMA. 2000;284:2599-2605* - November 22/29, 2000Vol 284, No. 20, pp 2551-2672

Vor Einführung der Triptane wurden häufig Ergotamine verordnet, heute spielen sie keine große Rolle mehr. Ihr Wirkmechanismus ist den Triptanen ähnlich, das Nebenwirkungspotential ist aber ungünstiger. Sie dürfen auf keinen Fall mit Triptanen kombiniert werden.

Kontraindikationen gegen Ergotamine Davidoff RA. Migraine: Manifestation, Pathogenesis, and Management. Philadelphia, PA: FA Davis; 1995.

- Periphere Arteriosklerose
- Koronare Herzerkrankung
- Thrombophlebitis
- Hypertonus
- Bradykardie
- Hohe Dosen Betablocker
- Leberfunktionsstörungen
- Hyperthyreose
- Mangelernährung
- Schwangerschaft und Stillzeit
- Infektionen und Fieber
- Alter über 60 Jahre (relative KI)

Langdauernde Auren mit neurologischen Symptomen sind ein bisher unbefriedigend behandelbares Syndrom, der NMDA-Rezeptor-Antagonist Ketamin kann bei einigen Patienten mit hemiplegischer Migräne die Ausbreitung blockieren (Kaube et al. Neurology 2000;55(1):139-41) und bei einzelnen Patienten mit visuellen Auren und Hirnstammauren mit Bewußtseinsstörungen war die Gabe von Naloxon bzw. Flumazenil erfolgreich (Sicuteri et al. Headache 1983;23:179-83; Requena et al. Rev Neurol 1999;29:1048-51, Einzelfallberichte liegen auch zu dem Diuretikum Furosemid vor. **T. D.** Rozen. Treatment of a prolonged migrainous **aura** with intravenous **furosemide**. Neurology 2000;55:732

Migräne- Kopfschmerzen bei Kindern:

Kopfschmerzen bei Kindern unterscheiden sich in den Symptomen nur wenig von denen bei Erwachsenen. Die Internationale Kopfschmerzklassifikation legt für die Einordnung des kindlichen Kopfschmerzes die gleichen Kriterien wie für Kopfschmerzen im Erwachsenenalter zugrunde, lediglich für Migräneattacken wird eine kürzere Dauer (2 Stunden im Vergleich zu 4 Stunden) gefordert. Bei kindlichen Kopfschmerzen sollten nicht medikamentöse und medikamentöse Behandlungsmaßnahmen kombiniert werden, und nicht medikamentöse Maßnahmen wie das Erlernen eines Entspannungsverfahrens oder verhaltentherapeutische Gruppenbehandlungen den Vorrang haben. Gelegentliche Kopfschmerzen hat fast jedes Kind: 83 % der 8 bis 9-jährigen bzw. 90 % der 11 bis 12-jährigen Kinder leiden gelegentliche an Kopfschmerzen. 60 % aller Kinder und Jugendliche leiden an Kopfschmerzen vom Spannungstyp, 10 bis 12 % unter Migräne. Erstmanifestation der Migräne ist meist zwischen 6. und 8. Lebensjahr. Mädchen sind nach dem Alter von 10 Jahren sind signifikant häufiger von Migräne betroffen als Jungen. Je früher sich Migräne manifestiert, desto wahrscheinlicher ist ein schlechter Verlauf. Bei etwa einem Viertel verschwindet die Migräne im Laufe der nächsten Jahre wieder. Sekundäre Kopfschmerzen im Kindesalter (meist infolge einer Infektion) werden häufig in Eigenregie von Eltern therapiert. Neben Bettruhe, Kühlung der Stirn, Entspannung, Unterbrechung der ursprünglichen Tagesaktivität, Reizabschirmung, Entspannung, ätherische Ölen oder Akupressur, kommen dabei medikamentös Paracetamol oder Ibuprofen in Frage. Für Ibuprofen gibt es eine bessere Studienlage und eher weniger Nebenwirkungen. Zur medikamentösen Attackentherapie der Migräne kommen wie bei Erwachsenen für leichte Migräneattacken, Ibuprofen, in Betracht. Auf Acetylsalicylsäure sollte bei Kindern wegen des Risikos eines Reye- Syndroms verzichtet werden. Paracetamol kann möglicherweise die Entwicklung von Allergien bei Kindern begünstigen. Bei sehr starken Migräneattacken können auch bei Jugendlichen Triptane erwogen werden. Bezüglich Metoclopramid ist wegen des relativ hohen Risikos von Dyskinesien eher abzuraten. Dringend empfohlen wird auch das Führen eines Kopfschmerztagebuches. Als Migräneprophylaxe kommen Metoprolol in Frage (Metoprolol 1 bis 2 mg pro kg Körpergewicht pro Tag, als abendliche Einmaldosis, wobei die Behandlungsdauer zwischen 4 und 6 Monaten liegen sollte).

Weiter Zurück

Spannungskopfschmerzen	Migräne allgemein
sogenannten medikamenteninduzierten Kopfschmerz.	Migräne was passiert im Gehirn
Cluster Kopfschmerzen	Migräne Behandlung der Attacke
cervikogener (von der Hals- Wirbel-Säule ausgehender) Kopfschmerz.	Migräne Vorbeugung
Tabellarischer Überblick über verschiedene Kopfschmerzsyndrome	Kopfschmerztagebuch zum ausdrucken als pdf
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ARTICLES

A nosographic analysis of the migraine aura in a general population

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The study presented here is the first detailed nosographic analysis of migraine aura, diagnosed using the criteria of the International Headache Society, in a sufficiently large sample for statistical analysis. Of 4,000 people, 163 had migraine with aura. Sixty-two had attacks of migraine aura with headache as well as migraine aura without headache, and seven had exclusively migraine aura without headache. Visual symptoms were most frequent (99%), followed by sensory (31%), aphasic (18%) and motor (6%) symptoms. Those with several types of aura symptoms had visual aura in virtually every attack, while sensory, motor and aphasic aura were present only in a small number of their attacks. The typical visual aura starts as a flickering, uncoloured, zig-zag line in the centre of the visual field and affect the central vision. It gradually progresses towards the periphery of one hemifield and often leaves a scotoma. The typical sensory aura is unilateral, starts in the hand, progresses towards the arm and then affects the face and tongue. The typical motor aura is half-sided and affects the hand and arm. The visual, sensory and aphasic auras rarely lasted > 1 h, while the motor aura did in 67% (six out of nine). Four people had exclusively acute onset visual aura. The duration of the aura and the characteristics of the ensuing headache were typical for migraine with aura, suggesting that acute onset aura is a real phenomenon. Headache followed the aura in 93%, headache and aura occurred simultaneously in 4% and aura followed headache in 3%. The characteristic spread of each symptom and the sequence of different symptoms suggest that cortical spreading depression is the mechanism underlying the migraine aura. Our results do not suggest that alterations of the diagnostic criteria of the International Headache Society are needed. The intra-individual variation of aura symptoms shown in this study indicates that a simplification of the International Classification of Diseases, Neurological Adaptation is appropriate.

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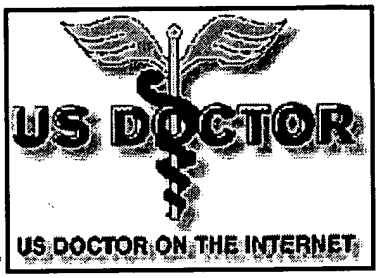

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TOPICS INCLUDED IN THIS ARTICLE

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The new classification of headache, prepared by the International Headache Society, has discarded the old terms of classical and non-classical (common) **migraine**, and replaced them, respectively, with **migraine** with aura and **migraine** without aura. These terms illustrate the major difference between these two entities, the presence of a prodrome or aura, occurring one hour or less before the onset of the acute attack. By definition, **migraine** is a unilateral headache that may become generalized. It does not occur on a daily basis, and rarely continues over 24 hours.

EPIDEMIOLOGY
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In a recent report, **migraine** prevalence was investigated in a sampling of 15,000 U.S. residents, aged 12 to 80 years.[1] Each of these households received a self-administered questionnaire which considered symptoms, frequency, and severity of headaches. Responses were received from 20,468 subjects (63.4%). In reviewing the replies, 17.6% of the females and 5.7% of the males were found to have one or

more **migraine** headaches annually. The authors projected that in the total U.S. population, estimates of 8.7 million females and 2.6 million males probably suffer from **migraine** headaches, with moderate to severe disability. Of these 3,4 million females and 1.1 million males experience one or more attacks per month. The impact on work days lost and expenditures for over-the-counter and prescription drugs is staggering. These migraineurs are more likely to utilize emergency treatment services for their acute attacks than the rest of the population.

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PATHOGENESIS
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Although **migraine** has been a recognized entity for centuries, debate continues over its pathogenesis. Wolff described **migraine** as a self-limited, neurogenic sterile inflammation[2] He identified the occurrence of four dynamic events during a **migraine** attack: 1) initial cerebral vasoconstriction, which is correlated with the aura or warning of **migraine**; 2)the extracranial vasodilation (which Wolff considered the cause of **migraine** pain); 3)the sterile inflammation that increases the pain and prolongs the **migraine** attack; and 4)a secondary muscle contraction.

Wolff suggested that the vasoconstriction occurring during the aura involves either the retina (or the retinal or ophthalmic artery), or the occipital portion of the cerebral hemisphere. During his investigations, he attempted to determine if there was a causal relationship between the initial cerebral vasoconstriction to the cranial vasodilation of **migraine**. He observed that cerebral vasoconstriction had usually ended before the extracerebral vasodilatation had started. Wolff suggested that dilatation and the distention of large arteries, as well as an increase in pain-threshold-lowering substances, produce the headache. During a **migraine** attack, the pain usually radiates from the large subsurface cranial arteries and their branches. The patient will experience pain if the vessels are distended, pulled upon, or displaced.

Through further investigations, Wolff postulated that a sterile inflammation occurs in addition to the vasodilatation. A neurokinin and a proteolytic (neurokinin-forming) enzyme neurogenically induce the inflammatory reaction. Five groups of substances, and possibly more, have been implicated with the sterile inflammation. These substances include catecholamines, histamine and serotonin, peptikinins, prostaglandins, and the slow-reacting substances of anaphylaxis (SRSA), an acidic lipid. Contraction and relaxation of smooth muscle are caused by these substances, in addition to constriction or dilatation of arteries and veins, induction of water and sodium diuresis, fever, wheal and flare reactions, and triggering of pain, including headache. in his studies, Wolff noted that noxious stimulation of any part of the head triggers muscle contraction of the head and neck. Therefore, noxious stimulation triggered by vascular distention will also cause muscle contraction. Sustained muscle contraction of the muscles of the head and neck can be triggered by emotional tension. This sustained contraction may persist after the vascular aspects of the headache have diminished, and is considered a secondary feature of the **migraine** attack.

Wolff's theories have been disputed by several researchers, including Olesen's group.[3] In their investigations, they injected a radioactive isotope, xenon-133, into the carotid artery, and induced **migraine** after arteriography in a series of subjects. They described a "spreading oligemia" which usually starts in the occipital regions and radiates anteriorly, reaching a primary sensorimotor area after the symptoms from that region had started. After the focal symptoms ceased, the oligemia continued. The authors, using this regional blood flow method, suggested that the painless pre-headache phase of **migraine** with aura was possibly secondary to a reaction similar to the spreading depression described by Leao and not secondary to oligemia.

In an earlier study, Olesen's group noted that the striking oligemia did not occur in **migraine** without

aura.[4] No significant change was demonstrated in cerebral or regional blood flow between the resting phase, the onset of migraine without aura, and the acute attack. Skyhoj Olsen reported on the limitations of these cerebral blood flow (CBF) studies[5] He proposed the "spreading oligemia" observed in CBF studies during migraine with aura may be an artifact that reflects a gradual decrease of CBF in an area of constant size. His theory suggests that migraine with aura and migraine without aura may be due to the same disease process but differ in the intensity of vasospasm and CBF reduction.

Local and systemic biochemical changes also occur during the headache phase. The preceding vasoconstriction phase causes local anoxia and acidosis. A systemic decrease in serotonin levels occurs as serotonin is transported by the blood vessels and the perivascular tissues. In response to local metabolic changes, the noninnervated parenchymal arteries dilate (a reaction also potentiated by the drop in blood serotonin), increasing cerebral blood flow and provoking local vasomotor changes in the innervated system of blood vessels, particularly marked dilation of the ipsilateral extracranial and intracranial arteries. Vasoactive substances, including serotonin, sensitized the pain receptors in the blood vessels and produces sterile inflammation around the vessels. These changes and the vasodilatation, cause the pain of migraine. This observation explains the hemicranial aspect of migraine.

In 1969, Heyck suggested that migraine is caused by the opening of carotid arteriovenous anastomoses, shunts, in the head,[6] When open, direct oxygenated blood will be diverted wastefully to the veins. The tissues requiring oxygen will be bypassed. The shunt vessels may divert large volumes of blood and become distended and pulsating. Heyck's theory helps support the effectiveness of a new specific subtype-selective serotonin agonist which terminates established migraine with minimal side effects. Recent investigations have advanced our understanding of 5-hydroxytryptamine (5-HT) receptors. These receptors are membranal "trigger" proteins with which 5-HT must interact to produce its various actions. It is possible to selectively stimulate only one type of 5-HT receptor by producing a selective synthetic 5-HT-like molecule, and thus mimic some actions of 5-HT.

CLINICAL FEATURES
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For most migraine sufferers, the initial onset of their headaches occurred during adolescence or their twenties. Migraine does occur in childhood, as noted by Bille in this study of school children that the average age of onset was six years old.[7] The initial onset of migraine rarely occurs after age 40. During the fifth and sixth decade of life, migraine usually disappears, often with the onset of menopause. Some patients with migraine with aura will experience the prodromes long after the headaches have stopped.

Sex Distribution

The higher incidence of migraine in females has long been recognized. In an earlier study by Linet's group, the authors noted the prevalence of migraine in the general population was 7.4% for females and 3% for men.[8] In childhood migraine, there is an equal distribution between the sexes but after puberty, the predominance in females is obvious.

Family History

Migraine has long been considered a familial disorder. Selby and Lance reviewed the histories of 464 patients and noted a 55% family history of migraine.[9] Researchers have not concluded if migraine is a hereditary or familial disorder. In my own clinical experience of over 30 years, a family history of

headache is reported by at least 70% of migraine sufferers.

Clinical Presentation

According to the definition established by the International Headache Society, migraine is "an idiopathic, recurring headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, photo- and phonophobia."[10] Migraine headaches do not occur on a daily basis, and the usual frequency is one to four per month. In some patients, the migraine may occur once yearly or as often as 15 to 20 times per month.

Characteristically, migraine affects one side of the head, and may switch sides. The headache can become generalized. Many patients indicated that the pain localizes around or behind the eyes, or in the front-temporal area. The pain may radiate towards the occiput or upper neck during an attack. The shoulder and lower portion of the neck may be involved. In some patients, the pain may radiate to the face.

The pain of migraine is often observed by the patient to start as a dull ache and develop into a throbbing and pulsating pain. Other patients will complain of a constant headache that is never pulsatile in nature. During the attack, the area over the dilated arteries may be tender, and this symptom may continue for several hours after the attack. The degree of severity is variable but migraine can be incapacitating. Migraine usually continues for 4 to 24 hours, although the attack may continue for one or more days. The patient may experience lethargy and fatigue for several days after an attack. Status migraine describes those attacks that are continuous for several days or weeks.

Migraine has often been described as a "sick" headache. Nausea and vomiting are frequent components of an acute attack. Other associated symptoms are anorexia, photophobia, phonophobia, constipation, diarrhea, dizziness, lightheadedness, blurred or double vision, chills, tremors, cold extremities, ataxia, and dysarthria. Difficulty in concentration and memory loss has been reported by some patients.

The prodromes occurring in patients with migraine with aura usually start one to two hours before the acute headache. The symptoms typically continue less than one hour. In order of frequency, the prodromes are: 1)scotoma (blind spots); 2) teichopsia (bright shimmering or wavy lines) or fortification spectra (a zigzag pattern resembling a fort); 3)flashing of lights (photopsia); 4)paresthesias; and 5)visual and auditory hallucinations (Alice in Wonderland Syndrome). The positive visual disturbances include photopsia, teichopsia, or the fortification spectra; the negative disturbances include scotomata; hemianopsia (partial visual field loss); or metamorphopsia (illusions of distorted size of shape). Other prodromal symptoms include paresthesias that occur as a "slow march" through the body.

Patients with migraine without aura may describe premonitions of an impending migraine attack. The vague symptoms may occur from two to 72 hours before an attack, and may occur four times as frequently as the prodromata of migraine with aura. These premonitions can occur in either type of migraine and include hunger, anorexia, drowsiness, depression, irritability, tension, restlessness, talkativeness, a surge of energy, and a feeling of well-being.

The Migraine Personality

The debate continues over the subject of "migraine personality." Wolff described migraine patients as ambitious, perfectionist, persistent, and unforgiving.[11] The children included in Bille's study were described as fearful, tense, sensitive, and easily frustrated.6 These findings confirmed the observations of Wolff. In 1976, however, Phillips reviewed several investigations and noted that evidence was limited to

support the theory that migraine sufferers were more neurotic than age-matched controls [12] Ross and McNaughton reviewed the Rorschach records of migraine patients, and observed a tendency towards rigidity, perfectionism, intolerance, conventionality, obsessive-compulsive features, persistence towards success, and difficulty in sexual adjustment.[13] From my own clinical experience, I would agree with the findings of their study as well as that of Wolff.[14]

Precipitating Factors

Although many migraine patients will experience difficulty in identifying migraine triggers, the use of a headache diary will facilitate this process. On this diary, patients will be asked to record the frequency, duration, and severity of the migraine attack, as well as any provocative factors which may have triggered the headache. Migraine triggers can be divided into three categories: 1) external stimuli; 2)physiological; and 3)psychological.

Stress is probably the most readily identified trigger of an acute migraine attack. Curiously, many migraine patients will remain headache-free during a stressful period only to experience a severe headache when the stress has resolved. Many migraine patients will create an environment too great to handle, such as the working mother who attempts to go back to school, and juggle the demands of a career, raising a family, and pursuing a degree. An increase in migraine frequency is inevitable. Depression, fear, anger, anxiety, and repressed hostility have also been identified as migraine provocateurs. Although avoiding stress is difficult to achieve, instruction on coping methods may be beneficial for these patients.

The migraine sufferer is especially sensitive to any changes in sleep and eating patterns. Fasting or missing a meal is a known headache trigger. All migraine patients should be encouraged to maintain a strict meal schedule. Oversleeping or lack of sleep can also precipitate a migraine, although migraine rarely awakens a patient. The incidence of headaches occurring on weekends, holidays, or during vacations has been linked to oversleeping. Headache clinicians believe that the responsible mechanism is a relative hypoglycemia or an alteration in the level of carbon dioxide. In order to avoid these "weekend" headaches, patients should be instructed to maintain a regular sleeping schedule, and plan on arising at the same time each day. Lack of sleep and fatigue may also provoke an acute migraine attack.

The link between diet and migraine has long been a controversial subject. Most physicians who participated in a survey regarding "dietary migraine" believed that the acute attacks were triggered by certain foods that contain vasoactive substances. The term diet-precipitated migraine has been allotted to these headaches. The direct-acting vasoactive substances are the amines, including tyramine, nitrates, monosodium glutamate, and alcohol. Tyramine is found in aged cheese, pickled foods, fresh-baked yeast breads, and marinated foods. Another amine, phenylethylamine, is contained in chocolate. The nitrates, which cause migraine due to their vasodilating action, are found in cured meats. Monosodium glutamate is found in food additive and Chinese foods, and can cause a variety of symptoms, including pressure in both central and direct vasodilating properties. Migraine can be precipitated by a single glass of red wine.

Indirect-acting vasoactive substances include caffeine, nicotine, ergotamine, hypoglycemia, allergy, ingestion of ice cream, and monoamine oxidase inhibitors. Caffeine and nicotine are vasoconstrictors. However, rebound vasodilation may evolve from intemperate ingestion of these substances. Excessive consumption of caffeine-containing beverages, such as coffee, tea, or colas, can precipitate a migraine attack. Predictably, caffeine withdrawal, often associated with fasting, can trigger a severe headache.

Some migraine patients will describe a relationship between their headaches and weather. Rapid changes in barometric pressure as well as extreme variations in weather may provoke a migraine attack.

During or subsequent to travel to areas of high altitude, a may report an increased frequency in their headaches. A diuretic, such as **acetazolamide**, used on the day of a flight may prevent these headaches.

A relationship between the menstrual cycle and **migraine** attacks is well documented. The increased incidence of **migraine** in women exemplifies this relationship. Of these female migraineurs, 60% to 70% will note a menstrual link to their **migraine** attacks, with severe headaches occurring immediately before, during, or after their period. Also, many of these women will note a remission in their headaches after the first trimester of pregnancy. Older patients will note a decrease or complete remission of their headaches after menopause. Oral contraceptives should be avoided in **migraine** patients as these drugs have been observed to increase the frequency, severity, duration, and complications of **migraine**. Also, estrogen replacement therapy should be avoiDed in post-menopausal migraineurs when giving these hormones exacerbates or restarts a **migraine** attack.

TREATMENT
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Drug therapy of **migraine** is difficult and will require frequent office visits and adequate lines of communication between the physician and the patient. Both the physician and the patient should have an adequate understanding of the complexities of treatment and the physician should be cognizant of drug interactions. Dependent on the patient's history, the physician must select the type of therapy indicated. If the patient is only experiencing occasional headaches, abortive treatment may be indicated. however, if the headaches are occurring two or more times per month, or if the attacks greatly impact on the patient daily life, due to absences from work or school, prophylactic therapy should be considered.

Abortive Therapy

Recently, a serotonin receptor agonist, sumatriptan, has demonstrated success in the abortive treatment of **migraine**. Sumatriptan acts as an agonist at the 5-HT(1D) receptor. The net effect of this action appears to be important in **migraine** as it causes the constriction of dilated arteries in the brain. Compared to serotonin itself, sumatriptan is safer and better tolerated by patients because its effect are highly specific are highly specific for this receptor. Also, sumatriptan may be advantageous over currently available agents for the treatment of **migraine** because of this specific effect on the 5-HT(1D) receptor as an agonist.

This agent, administered subcutaneously in doses of 6mg produced beneficial effects in treating **migraine** attacks.[14] This dose may be repeated after one hour if symptoms return. Side effects associated with this therapy included tingling, dizziness, warm-hot sensations, and injection-site reactions. Intravenous sumatriptan administration is contraindicated due to the potential of to cause coronary vasospasm. Sumatriptan should not be administered subcutaneously in patients with ischemic heart disease, prior history of myocardial infarction, documented silent ischemia, or patients with Prinzmetal's angina. Sumatriptan may cause increases in blood pressure and is therefore contraindicated in patients with uncontrolled hypertension. It should never be used concomitantly with ergotamine preparations. Studies are currently underway on the oral preparation of this drug in the treatment of acute **migraine**.

The ergotamine preparations have been used in **migraine** abortive therapy for several decades. These drugs are classified as vasoconstrictors that specifically counteract the dilation of some arteries and arterioles, primarily the branches of the external carotid artery. The success of ergot in a **migraine** attack impinges on early use of the drug during an attack or preferably during the prodromal phase. Ergotamine is available in preparations suitable for various routes of administration, including oral, sublingual, rectal, and parenteral. Selecti·g the route of administration is dependent on the following: 1)need for

rapid actin; 2)associated nausea and vomiting; 3)availability of the preparation; and 4)the patient's preference.

Nausea is a frequent side effect of ergot preparations and caffeine has been added to the oral and rectal preparations in order to facilitate absorption of the drug, and ergot and caffeine are believed to act synergistically. Sublingual preparations should be considered if the oral route is too slow or is not tolerated. The rectal suppository is the most effective of the non-parenteral preparations and is especially helpful for those patients with associated vomiting. However, its use may be awkward for the patient and should not be used in those migraineurs with associated diarrhea. The parenteral form of ergotamine is no longer available in the U.S. However, an ergotamine derivative, dihydroergotamine (DHE-45) may be used IV or IM.

In order to prevent ergotamine rebound phenomena, a four day hiatus must be maintained between days of use of these agents. Ergotamine should never be repeated on the second or third day of a **migraine** attack. If the drug is stopped abruptly, the patient will experience a severe rebound headache. Excessive consumption of the ergots may cause symptoms of vasoconstriction, such as cold, clammy extremities, and could lead to ergotism.

Patients with peripheral vascular disease, thrombophlebitis, severe hypertension, coronary ischemia, angina, renal or hepatic disease, or recent infection should not use an ergotamine preparation. These agents should not be used in the elderly, or during pregnancy because of the oxytocic effects of ergotamine. The us of a combination agent containing isometheptene mucate, dichloralphenazone, and acetaminophen (Midrin) may be indicated for those patients who cannot use the ergots. Isometheptene has cerebral vasoconstrictor action.

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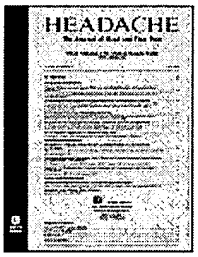

Abstract

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Migraine With Aura During Pregnancy

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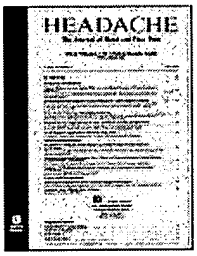

Abstract

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Aborting a Prolonged Migrainous Aura With Intravenous Prochlorperazine and Magnesium Sulfate

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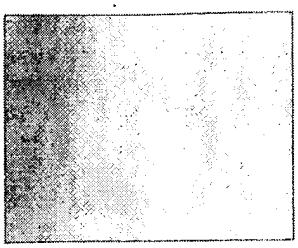

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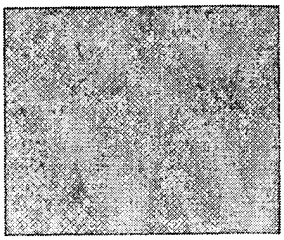

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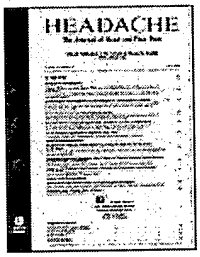

Abstract

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Aborting a Prolonged Migrainous Aura With Intravenous Prochlorperazine and Magnesium Sulfate

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The Practical Peer-Reviewed Journal for Primary Care Physicians

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A fresh look at migraine therapy

New treatments promise improved management

Seymour Diamond, MD

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CME learning objectives

- To become familiar with the pathophysiology and clinical features of **migraine**
- To learn the common signs of various types of **migraine**
- To understand the various options available for acute and prophylactic therapy of **migraine**

Dr Diamond discloses financial interests in or connection with the following pharmaceutical companies: Glaxo Wellcome, Wyeth-Ayerst, Bayer, Merck, AstraZeneca, Carnrick, Bristol-Myers Squibb, and Abbott.

This is the second of four articles on headache

This page is best viewed with a browser that supports tables.

Preview: About 26 million Americans, nearly 70% of them women, are challenged by persistent, sometimes incapacitating **migraine** headaches. Although treatment has

improved dramatically during the last decade, **migraine** headaches continue to raise diagnostic dilemmas and management questions among primary care physicians. In this article, Dr Diamond discusses diagnosis, current management, and prophylactic measures that can offer hope to many patients.

*Diamond S. A fresh look at **migraine** therapy: new treatments promise improved management. Postgrad Med 2001;109(1):49-60*

The malady known as **migraine** was identified thousands of years ago and is known throughout all civilizations on earth. The earliest recorded description of headache dates to Mesopotamia in 4000 BC. Aretaeus of Cappadocia (130 to 200 AD) devised the first true description of **migraine** as a distinct entity because of its unilateral occurrence, association with nausea, regular recurrence, and paroxysms of pain separated by pain-free intervals. Because the pain was unilateral, Aretaeus called this type of headache "heterocrania." We now use the word "hemicrania," which literally means "half a head." Aretaeus also recognized the differences between acute headache attacks that lasted for days (cephalalgia) and chronic headaches (cephalea).

Classification of headache

Many elaborate classifications of headache have been formulated, including the 1962 recommendations of the Ad Hoc Committee on Classification of Headache of the National Institutes of Health (1). The most recent effort was published in 1988 by the International Headache Society (2). These classifications are complex and lengthy and are used primarily for research purposes. Therefore, they are difficult to translate into clinical practice.

My colleague Donald J. Dalessio, MD, and I devised a practical classification of headache for clinical use (3). We classified headaches into three primary categories (table 1): vascular (**migraine**, cluster) headache, tension-type (muscle contraction) headache, and organic (traction, inflammatory) headache. We also subdivided **migraine** into three types: **migraine** with aura (classic), **migraine** without aura (common), and complicated **migraine** (hemiplegic, ophthalmoplegic, and basilar artery **migraine**).

Table 1. Classification of headache

Vascular
Migraine
With aura
Without aura
Complicated
•Hemiplegic
•Ophthalmoplegic
•Basilar artery Cluster (histamine)
Toxic vascular
Hypertensive

Tension-type (muscle contraction)
Depressive equivalents and conversion reactions
Chronic anxiety states
Cervical osteoarthritis
Chronic myositis

Organic
Mass lesions (tumors, edema, hematomas, cerebral hemorrhage)
Diseases of eye, ear, nose, throat, and teeth
Arteritis, phlebitis
Occlusive vascular disease
Atypical facial pain
Temporomandibular joint dysfunction
Cranial neuralgias (facial, glossopharyngeal)

A large number of patients have coexisting **migraine** and tension-type headache, which we consider an overlapping category. This combination headache is sometimes called mixed headache syndrome, transformed **migraine**, or chronic daily headache. Patients who have these headaches usually can differentiate the severe headache that has **migraine** characteristics and occurs two to five times a month from the chronic daily headache that is less severe (4).

Pathophysiology

Although the pathophysiology of **migraine** has not been firmly established, we owe a great deal of our knowledge about **migraine** pathophysiology to Harold G. Wolff, MD. During the 1930s, Dr Wolff did extensive research on **migraine**, including performing a craniotomy on a patient who was having an acute **migraine** attack. He observed initial cerebral vasoconstriction, followed by extracranial and intracranial vasodilation (5). He also noted that sterile inflammation surrounded the affected vessel and secondary muscle contraction was present.

On the basis of this information, Dr Wolff formulated the vascular theory of **migraine**. He also noted that certain vasoactive substances found in the inflamed tissue around the blood vessels contained catecholamines, histamine, serotonin, peptides, prostaglandins, and the slow-reacting substance of anaphylaxis, which is an acidic lipid. Dr Wolff speculated that prolonged **migraine** attacks (lasting 24 to 48 hours) seemed to be related to sterile inflammation. As a result of Dr Wolff's findings, corticosteroids were used for treating prolonged **migraine** headaches.

The work of Sicuteri and associates (6) and Curran and colleagues (7) confirmed the role of serotonin and its metabolites during all phases of a **migraine** attack. These investigations demonstrated that serotonin-releasing agents can induce migrainelike attacks. The fact that many of the newer drugs used for management of acute **migraine** are serotonin receptor agonists further implicates serotonin as a key player in **migraine** pathogenesis.

Neurologic theories of **migraine** have also been proposed. Studies by Olesen and associates (8) suggested that **migraine** results from an abnormal firing of a brain neuron. Spreading depression, a part of the neurologic theory, could explain the prodrome or aura of **migraine**. Moskowitz (9) identified the trigeminal ganglion as a factor in inducing neurogenic dural inflammation and the subsequent vascular pattern of the **migraine** attack. Other, more recent investigations suggested that substance P (10), calcitonin (11), and nitric oxide (12) are all active in the dural inflammatory cascade that occurs with or causes the vascular changes.

Definition of migraine

Although several definitions of **migraine** have been formulated, we rely on the definition developed by the World Federation of Neurology (13). It defines **migraine** as "a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency, and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea, and vomiting. In some cases, they are preceded by, or associated with, neurological and mood disturbances."

The definitive characteristic of **migraine** with aura is the occurrence of a neurologic symptom complex 5 to 30 minutes before the onset of an acute **migraine** attack. Complicated **migraine** is described as a **migraine** attack associated with focal neurologic symptoms that may persist after the headache disappears. Ophthalmoplegic, hemiplegic, and basilar artery **migraine** are considered forms of complicated **migraine**.

Among adults who have **migraine**, about 70% are women and, of those, about 70% report a relationship between acute **migraine** attacks and menstruation. Menstrual **migraine** attacks can occur immediately before, during, or after menses. However, some women may also have attacks at other times of the month. Many women report a decrease in or complete remission of **migraine** attacks after the first trimester of pregnancy.

Clinical features

Migraine is not a daily headache. Frequency varies from a few headaches each week to one or two episodes each year. Most often, attacks occur two to eight times a month. Average duration is 4 to 24 hours, although some patients complain of headache lasting several days (status migrainosus). The degree of severity varies from moderate to incapacitating.

Patients who have **migraine** headaches often describe them

as throbbing or pulsating. Although **migraine** pain is usually unilateral, it can occur on both sides of the head. Pain often affects the frontal and temporal regions but may be localized behind the eye. Also, pain can radiate across the head and to other regions of the face and neck.

Because of its association with nausea, vomiting, photophobia, phonophobia, dizziness, tinnitus, and blurred vision, **migraine** is often depicted as a "sick" headache. Symptoms can influence the selection of abortive and pain-relieving medication, as well as the route of administration. **Migraine** headaches are often exacerbated by physical activity.

Although **migraine** can first occur in childhood or as late as age 50, it usually starts during adolescence or young adulthood. In childhood **migraine**, boys and girls are affected equally until puberty, when the predominance shifts to girls (60% to 70%). Up to 70% of migraineurs report a family history of similar headaches.

The warning phase

As stated earlier, the two major types of **migraine** are differentiated by the presence of an aura (prodromata). The aura consists of focal neurologic symptoms localized to the cerebral cortex or brainstem that may initiate or accompany the headache phase. Symptoms develop gradually over 5 to 20 minutes and are attributed to initial vasoconstriction. The aura typically lasts less than an hour.

The symptoms of the aura usually include such visual phenomena as flashing lights, zigzag or jagged lines, blind spots, difficulty in focusing, and distorted perception. Sometimes visual images are out of focus or appear to be unusually large or small.

Another occasional warning symptom is difficulty in speech, such as inability to find the right word or use of wrong words. A complete inability to speak occurs on rare occasions. Some patients are not able to understand what has been said. Also, headache may be preceded by motor aphasia.

Some patients who have **migraine** attacks, with or without aura, also have vague premonitory symptoms that start from 12 to 36 hours before the actual headache occurs. The symptoms usually begin imperceptibly and develop slowly. Premonitory symptoms vary and may range from one extreme to the other (eg, from euphoria to withdrawal, hyperactivity to sluggishness, extreme hunger to anorexia, diarrhea to constipation, frequent urination to fluid retention).

Other premonitory symptoms include yawning and fatigue, difficulty focusing, changes in personality, slurred speech, impaired concentration, irritability, agitation, sensitivity to light or sound, stiff neck, general muscle weakness, sensitive skin, and thirst. Some people have a feeling of well-being, become unusually talkative, and notice a surge of energy. The person's face may be pale, and the eyes may appear dark, heavy, or sunken. Although the **migraine** victim is not aware of these warning signs, friends or relatives may notice them.

Variations in hormone levels trigger headaches in many

women, and fatigue, oversleeping, or skipping a meal can bring on **migraine** in some people. Medications have also been implicated in **migraine** attacks, including such agents as nitroglycerin, reserpine, indomethacin (Indocin), oral contraceptives, and cyclic estrogen replacement drugs. Psychological factors, such as anxiety, depression, repressed hostility, anger, and fear, can play a role as well.

Treatment

Migraine treatment can be divided into four types: general measures, abortive therapy, pain relief measures, and prophylactic therapy. Status migrainosus may require that additional strategies be tried.

General measures

An important step in **migraine** management is identifying and avoiding headache triggers. Because **migraine** patients are particularly sensitive to changes in routine, regular sleep and meal schedules should be maintained. Although stress cannot be avoided, training in coping strategies or stress management may be beneficial. Similarly, a significant number of **migraine** sufferers appear to be obsessive, compulsive, and rigid, although this hypothesis has been debated. They may create environments that present enormous challenges. For example, a working mother returns to school and also participates in a number of volunteer activities. In many cases, a **migraine** sufferer endures a stressful period but then has a severe headache once the stress is alleviated.

Certain activities often trigger acute **migraine** attacks, such as looking at bright lights or the sun or watching a flickering or out-of-focus television program or film. I recommend use of tinted glasses during times of exposure to bright light for my **migraine** patients. In addition, flying or being at high altitudes, where the oxygen tension and concentration are usually lower than normal, can precipitate **migraine** attacks. **Acetazolamide** (Dazamide, Diamox), a diuretic and carbonic anhydrase inhibitor, taken the day before and the day of flying, may help patients who have **migraine** related to altitude changes. Changes in barometric pressure have also been identified as a **migraine** trigger, and **migraine** patients may be especially sensitive to weather conditions.

Abortive therapy

Until the early 1990s, only a few drugs were available for the acute treatment of **migraine**. Many physicians started with over-the-counter analgesics or prescription nonnarcotic nonsteroidal anti-inflammatory drugs (NSAIDs), progressed through the ergotamine drugs, and used narcotics as a last resort in patients who had acute **migraine** attacks. Many times, management involved a litany of trial and error before a suitable drug was found. With the introduction of the triptans, early intervention with these **migraine**-specific drugs may act to reverse the **migraine** cascade.

Since then, advances have been made in pharmacologic therapy for **migraine**. Nevertheless, management of the **migraine** patient still requires frequent office visits, open communication between physician and patient, and an understanding by both physician and patient of the intricacies of drug treatment and interactions. For example, the route of administration is important in obtaining relief because it

impacts the speed of action. Although oral administration is the simplest, it may not be appropriate for many of the 70% of migraineurs who have associated nausea and vomiting. Parenteral administration offers the quickest action, but self-injection may not be the optimal choice for many patients. A trip to the physician's office or emergency department delays the relief so badly needed.

Triptans: Discovery of the 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonists ("triptans") has brought about remarkable advances in the treatment of **migraine** (14). These drugs have demonstrated efficacy in aborting **migraine** attacks and have variable affinity for the 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1F}$ receptors. Their antimigraine effect is exerted by way of a receptor-mediated neural pathway in both the central nervous system and the trigeminal nerve, at which point neurogenic inflammation is blocked.

Sumatriptan succinate (Imitrex), the first triptan to be approved for **migraine** abortive therapy in the early 1990s, originally was available only for subcutaneous injections. Now sumatriptan can be given by oral or intranasal routes, as well as by injection. It is usually well tolerated and causes only minor side effects (eg, flushing, tingling, neck or chest tightness or pain, nausea, throat discomfort). If the first dose of sumatriptan offers at least partial headache relief, a second dose can be given an hour later or anytime within the next 24 hours if the headache recurs. However, a 5-day hiatus should be maintained between days of use. Sumatriptan should not be used in patients with basilar or hemiplegic **migraine**, ischemic heart disease, or Prinzmetal's angina and cannot be used concomitantly with ergotamine preparations or monoamine oxidase inhibitors (MAOIs).

Several oral second-generation 5-HT$_{1B/1D}$ agonists have been developed in the past few years. In 1998, the US Food and Drug Administration (FDA) approved naratriptan (Amerge), rizatriptan benzoate (Maxalt, Maxalt-MLT), and zolmitriptan (Zomig) for **migraine** therapy. It should be noted that none of the triptans can be used concomitantly with ergotamine derivatives nor should they be used in patients with basilar or hemiplegic **migraine**, ischemic heart disease, or Prinzmetal's angina.

Naratriptan has a longer half-life than the other triptans and remains active in the blood vessels for up to 6 hours. It has a low incidence of side effects, the most common of which are nausea and vomiting. Naratriptan holds promise for management of menstrual **migraine** because it has a long half-life. In addition, it can be used with MAOIs.

Rizatriptan is absorbed rapidly, and its effects can be noted within 30 minutes of ingestion. It is well tolerated but can cause a few mild side effects (eg, bitter taste, dizziness, fatigue, sleepiness, nausea). Rizatriptan is the only triptan currently available in an orally disintegrating tablet, which offers patients a convenient alternative if they prefer not to take water with their **migraine** medication. The formulation quickly dissolves on the tongue and is absorbed through the gastrointestinal tract. It does not exacerbate the nausea often associated with an acute **migraine** attack.

Zolmitriptan is also absorbed quickly and alleviates **migraine**

attacks faster than some of the other triptans. It appears to be effective in alleviating associated symptoms, including nausea and sensitivity to light and sound. Its side effects are similar to those with sumatriptan and include nausea, dizziness, prickling or tingling of the skin, drowsiness, warm or cold sensations, jaw pain, and tightness of the neck or throat.

Three new triptans (eletriptan [Relpax], almotriptan, frovatriptan) may be available in the near future.

Ergotamine derivatives: Ergotamine tartrate preparations are vasoconstrictors that have been used in **migraine** abortive therapy for more than 50 years. These agents are available for oral administration in combination with caffeine. Ergotamine is also available for sublingual administration, but in the United States, it is no longer available in the parenteral form. An adequate dose should be taken as early as possible in a **migraine** attack to achieve a maximum response.

To prevent ergotamine rebound headaches or ergotism, care should be taken to remain within the limits of the recommended dosage. Ergotamine derivatives should not be used in patients with cerebrovascular, cardiovascular, peripheral vascular, ischemic heart, renal, or hepatic diseases; sepsis; or severe hypertension. In addition, ergotamine preparations should be used cautiously in patients with peptic ulcer and recent infection and should not be used in pregnancy.

Dihydroergotamine mesylate (D.H.E. 45, Migranal) has also been used safely and effectively in the abortive therapy of **migraine**, and it has recently been "rediscovered" because of its action as a 5-HT_{1D} receptor agonist. It also has a potent effect at a number of other biogenic amine receptor sites. Unlike ergotamine tartrate, dihydroergotamine is associated with a lower incidence of nausea and is more of a venoconstrictor than an arterial vasoconstrictor. It can also be used to help patients who are ergotamine-dependent withdraw from ergotamine use.

Dihydroergotamine is available for intramuscular, subcutaneous, and intravenous injection and as a nasal spray. It also has been successfully used in repeated intravenous doses in patients with intractable **migraine**; a dose of 0.5 mg given as an intravenous push over 2 to 3 minutes, in combination with 10 mg of the antiemetic/antivertigo drug metoclopramide, may be repeated every 8 hours for 3 days in these cases.

Because of its vasoconstrictive properties, dihydroergotamine is contraindicated in patients who have peripheral vascular disease, ischemic heart disease, Prinzmetal's angina, uncontrolled hypertension, hemiplegic or basilar **migraine**, impaired hepatic or renal function, or sepsis, as well as in pregnant women. It should not be used concomitantly with other 5-HT_1 agonists or ergotamine preparations. Also, dihydroergotamine should not be given to patients who have risk factors for coronary heart disease (CAD) unless a cardiovascular evaluation provides satisfactory clinical evidence that a patient is reasonably free of CAD, ischemic myocardial disease, and other significant cardiovascular disorders.

For patients with risk factors predictive of CAD who have a satisfactory cardiovascular evaluation, the first dose of dihydroergotamine should be given in a physician's office. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining an electrocardiogram after the first dose is given to a patient with known risk for CAD.

Isometheptene mucate: In patients who cannot tolerate ergotamine or in whom ergotamine derivatives are contraindicated, isometheptene may be an effective alternative. Like ergotamine, isometheptene has cerebral vasoconstrictive actions. It is available in a preparation that also contains acetaminophen and dichloralphenazone, a mild sedative.

Aspirin and NSAIDs: Aspirin and other of the NSAIDs (eg, ibuprofen, naproxen sodium) have been used successfully in **migraine** abortive therapy. NSAIDs stabilize proteins and inhibit formation of active prostaglandins. They also inhibit inflammation through their effects on chemotaxis, phagocytosis, lysosomal enzyme release, and kinin generation.

Phenothiazines: The phenothiazines chlorpromazine hydrochloride (Thorazine) and prochlorperazine (Compazine) have been used effectively in the emergency department setting for the abortive treatment of acute **migraine**. Efficacy of these drugs is attributed to their antinauseant and sedative effects. In addition, their dopaminergic and adrenergic actions may trigger specific mechanisms involved in aborting **migraine**.

Lidocaine: A recent report (15) has suggested that use of intranasal lidocaine is helpful for abortive treatment of acute **migraine**. A 50% reduction in headache was noted by 55% of patients who used lidocaine. However, relapse was common and occurred early after treatment. In selected patients, this treatment has demonstrated significant benefit.

Pain relief measures

Abortive therapy may not completely resolve a **migraine** attack, and analgesics may be needed to alleviate pain. Over-the-counter analgesics (eg, aspirin, acetaminophen, ibuprofen, naproxen sodium, ketoprofen) may be effective. However, overconsumption of these analgesics, particularly those containing caffeine, can produce serious side effects. Withdrawal from caffeine-containing drugs may trigger caffeine withdrawal headache. Therefore, these drugs should be avoided in patients who have frequent **migraine** attacks.

The first over-the-counter agent approved by the FDA for relief of **migraine** pain was the combination of aspirin, acetaminophen, and caffeine (Excedrin **Migraine**). This combination agent is suggested for the acute treatment of mild to moderate headache without associated vomiting and disability. Recently, two other nonprescription preparations of ibuprofen (Advil **Migraine**, Motrin **Migraine**) have also received approval for the relief of **migraine** pain. In addition, a parenteral NSAID, ketorolac tromethamine (Toradol), offers analgesia that is nonnarcotic and nonhabituating, and it has a low side-effect profile. The drug is given intramuscularly in a 60-mg dose.

Among the other options for pain relief are use of narcotic analgesics, antiemetics, phenothiazines, and cold packs. Narcotic analgesics (eg, codeine, meperidine hydrochloride [Demerol HCl], methadone hydrochloride [Dolophine HCl, Methadose]), preferably administered parenterally, are effective for pain relief but are potentially habituating. As with other pain syndromes, these drugs should not be used in patients with frequent **migraine** attacks and should never be used for daily headaches.

Antiemetics and phenothiazines, given parenterally or rectally, may be indicated in some **migraine** patients. The phenothiazines (including promethazine hydrochloride [Anergan, Phenergan], chlorpromazine, and prochlorperazine) are also useful because of their sedative and antinauseant action. Some antiemetics, such as trimethobenzamide hydrochloride and metoclopramide, have little sedative effect. However, metoclopramide, a 5-HT_3 receptor agonist, enhances absorption of oral medications and has been used effectively in combination with intravenous dihydroergotamine. This use of metoclopramide occasionally causes nervousness and tremor.

Transnasal butorphanol tartrate (Stadol NS) is a totally synthetic mixed agonist-antagonist opioid analgesic that originally was available for parenteral administration. Its quick absorption through the nose is enhanced by its lipophilic nature. The highly vascular character of the nasal mucosa speeds uptake and absorption. Caution must be exercised because of the possibility of habituation to butorphanol, and it should not be prescribed for patients who have daily headaches.

Cold packs have been used by **migraine** patients for many years. Application of ice bags or commercially manufactured ice packs to the site of the pain, along with gentle pressure, may reduce the pulsating pain associated with acute **migraine** attacks.

Prophylactic therapy

Prophylactic drug therapy should be considered in patients who have more than two acute **migraine** attacks per month. It may also be considered in patients who have attacks that seriously compromise daily activities or that last several days.

Beta blockers: For the past two decades, the beta blockers have been recognized for their efficacy in **migraine** prevention. Researchers have suggested that beta blockers without intrinsic sympathomimetic activity are more beneficial than those possessing such activity. Propranolol hydrochloride (Betachron E-R, Inderal), timolol maleate (Blocadren), and nadolol (Corgard), all of which lack intrinsic sympathomimetic activity, are recognized as effective **migraine** prophylactic agents. Each of these drugs is considered nonselective and should not be used in patients with pulmonary disorders.

For patients with asthma and other respiratory disorders, treatment with a cardioselective beta blocker, such as metoprolol (Lopressor, Toprol XL), is indicated. Beta blockers are also contraindicated in patients with congestive heart failure and atrioventricular conduction disturbances. In addition, beta blockers should be used cautiously in patients

who use insulin, oral hypoglycemics, or MAOIs.

Antic nvulsant drugs: Divalproex sodium (Depakote) has shown efficacy in **migraine** prophylaxis. It may be of particular use in migraineurs with concomitant convulsive disorders, because it has the potential for preventing seizures. Divalproex should be avoided in patients who have a history of hepatitis or abnormal liver function. Recently, an extended-release formulation that can be used once a day received FDA approval.

NSAIDs: The use of NSAIDs has become increasingly common for prophylactic management of **migraine**. Acceptance of NSAID therapy was accelerated by the results of a randomized study of more than 22,000 male physicians who used low-dose aspirin or placebo every other day (16). About 6% of those on active medication had **migraine** attacks, compared with 7.4% of the placebo group. Although this decrease in headache frequency (20%) was modest, the results suggest that NSAID therapy may be effective in **migraine** prevention. Several NSAIDs have demonstrated prophylactic efficacy in decreasing the frequency and severity of **migraine**.

Calcium channel blockers: Calcium channel blockers may be considered in **migraine** prophylaxis, particularly in patients refractory to beta blocker therapy. The rationale for using these agents stems from their effect on intracranial vasoconstriction. Nimodipine (Nimotop) appears to have marked selectivity for the cerebral vasculature, and verapamil hydrochloride (Calan, Isoptin, Verelan) has also demonstrated antiplatelet effects.

Alpha-adrenergic blockers: For patients who experience food-related **migraine**, clonidine hydrochloride (Catapres) has demonstrated efficacy. Clonidine, an alpha agonist, has also been observed as beneficial for patients undergoing opiate withdrawal.

Antidepressants: Antidepressants have shown continued efficacy in **migraine** prophylaxis for several decades. The tricyclic drugs, particularly amitriptyline hydrochloride (Elavil), are believed effective in headache prevention because of analgesic actions independent of their antidepressant effects. Use of antidepressants is preferred for the treatment of coexisting **migraine** and tension-type headaches. Antidepressant therapy also may prove helpful in patients refractory to other standard forms of treatment. In these patients, a trial of the MAOIs should be considered.

Antihistamine and serotonin blockers: Cyproheptadine hydrochloride (Periactin) is the agent of choice in childhood **migraine** because it blocks both histamine and serotonin receptors. Side effects include drowsiness and weight gain. Efficacy in adults is minimal.

Methysergide: A lysergic acid derivative, methysergide maleate (Sansert) is closely linked to ergotamine. In addition to its vasoconstrictor actions, methysergide also appears to block the inflammatory mechanisms of serotonin. Although it has shown efficacy in **migraine** prevention, it is not widely used because of its serious side effects with prolonged therapy. When it is used, patients should be evaluated at monthly intervals to rule out pulmonary, coronary, or retroperitoneal fibrosis, as well as peripheral vascular

disease. If a patient has been maintained on methysergide for 6 consecutive months, a 4- to 6-week drug hiatus must be ordered and an intravenous urographic study should be performed to rule out retroperitoneal fibrosis.

Status migrain sus

In patients who have this disorder, **migraine** attacks are unrelenting and refractory to conventional therapy. For some **migraine** attacks that persist for more than 24 hours, the treatment of choice is adrenocorticosteroid therapy, such as dexamethasone or methylprednisolone in dose packs. Sterile inflammation is considered the cause of these prolonged **migraine** attacks.

When **migraine** persists, the associated symptoms (eg, nausea, vomiting) may pose a threat to the patient's well-being. Dehydration can become a problem, and hospitalization may be needed for intravenous fluid replacement and to monitor serum electrolytes. Intravenous dihydroergotamine (0.5 mg) given with metoclopramide (10 mg) every 8 hours for 2 days has demonstrated efficacy in treating status migrainosus. This therapy avoids use of habituating narcotic analgesics.

Summary

Successful management of **migraine** headaches involves identifying and avoiding headache triggers and using appropriate abortive therapy once a headache is recognized. Pain relief measures include over-the-counter analgesics, parenteral NSAID therapy when needed, and use of antiemetics and cold packs. Narcotic analgesics are best used only as a "last resort" measure.

Prophylactic therapy should be considered for patients who have more than two acute **migraine** attacks each month or whose daily activities are seriously compromised by headaches. For the patient in whom status migrainosus threatens well-being, hospitalization and more intensive therapy may be needed.

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For a helpful guide to electronic and print resources on headache for physicians and patients, see the Resource Guide in this issue.

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